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PHARMACOLOGY

Textbook

In two parts

Part 2

Recommended by the Academic Council of Sumy State University

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Material of the textbook is given according to the Training Programme in Pharmacology and Medical Prescription. Questions of general and special pharmacology are described at the up to date level. The textbook contains mechanisms of action, pharmacokinetics, pharmacodynamics, indications and contraindications for clinical use, and side effects of main groups of pharmacological drugs. The main attention is paid to data having fundamental meaning for training future doctors.

For students of higher medical educational institutions of the IV level of accreditation.

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INTRODUCTION

Presently, a large number of drugs are used to treat and prevent different diseases. Doctor of any speciality should be able to know them well for correct prescribing pharmacotherapy to patients. In this regard, there is a need for quality training of students of higher medical educational institutions in pharmacology, knowledge of which is basic and integrates theoretical and clinical disciplines. Pharmacology finishes theoretical training of future doctors and is a logical continuation of courses of normal and pathological physiology, biochemistry, microbiology, and anatomy. Therefore, the authors, when presenting the material, considered it necessary to briefly recall physiological, biochemical, immunological, and anatomical knowledge that is necessary for understanding of pharmacodynamics of drugs and their mechanisms of action.

Suggested textbook contains main rules of drug prescription, data of general and special pharmacology. With the aim to form stable skills in students to work with drug nomenclature, the unified nomenclature system of drugs, based on International Nonproprietary Names (*INN*), is given in the textbook. This system is used in modern educational literature of different countries. In most cases, the authors indicate both INN and most commonly used trade names of drugs.

All chapters of the textbook are given in volume that is necessary for clear understanding of principles of action and effective and safe use of drugs. Each pharmacological group is constructed in a unified and logical sequence which facilitates the perception, assimilation and use of information.

Due to large volume of information which should be mastered by students, the authors focus on group properties of drugs and describe the main representatives of groups. At the same time, the same drugs, used for different indications, are described in different chapters (e. g., β-adrenergic antagonists are given in chapters “Antiadrenergic drugs”, “Drugs for treatment of hypertension”,

“Drugs for treatment of ischemic heart disease”, and “Antiarrhythmic drugs”).

Main data about drugs are given in one main chapter, and additional information is given in other chapters. Data about pharmacodynamics, pharmacokinetics, clinical applications, and side effects are given for each group of drugs; and, if it is necessary, corresponding data about individual drugs are additionally given.

Suggested textbook contains data about new drugs and modern scientific data. Mechanisms of action and therapeutic indications for drugs are given considering modern data of biochemistry, pathological physiology and fundamental pharmacology. This textbook contains some elements of clinical pharmacology.

A separate chapter of the textbook describes general principles of treatment of acute poisoning by drugs and other toxic substances. Measures to prevent the ingress of poison into the body, inactivation of poisons by antidotes, restriction of poisons action by physiological antagonists, acceleration of poison elimination from the body, and resuscitation measures are given in this chapter. Besides, resuscitation measures at cases of inhibited respiration, collapse, acute heart failure, and bronchoconstriction are considered, especially in acute period of poisoning.

The textbook is recommended for third year students of higher medical educational institutions. Its structure and content correspond to the curriculum of pharmacology, approved at an interdepartmental meeting of heads of pharmacological departments of higher medical educational institutions.

We will be grateful for any comments and suggestions that may arise from the readers of this textbook.

DRUGS INFLUENCING INNER ORGANS

DRUGS INFLUENCING RESPIRATORY SYSTEM

Drugs used in different acute and chronic diseases of respiratory organs are classified into the following groups:

1. Drugs which are used in bronchial obstruction syndrome.
2. Expectorant drugs.
3. Antitussive drugs.
4. Breathing stimulators.
5. Drugs which are used in acute respiratory insufficiency.

Drugs Used in Bronchial Obstruction Syndrome

Bronchial obstruction syndrome is condition which is accompanied by recurrent attacks of expiratory dyspnea (difficult exhale) owing to spasm of bronchial smooth muscles, oedema of bronchi, and increased bronchial secretion.

In 2/3 cases, the cause of bronchial obstruction syndrome is bronchial asthma.

There are two forms of asthma:

– atopic (allergic);

– nonatopic (infectious).

Drugs used in bronchial obstruction syndrome are classified into three groups:

1. Bronchial spasmolytics.
2. Drugs eliminating the oedema of bronchial mucous membrane:

– stabilizers of tissue basophil membranes;

– glucocorticoids;

– drugs influencing leukotrienes system:

a) leukotriene receptor antagonists;

b) inhibitors of leukotriene synthesis.

3. Expectorants and mucolytics.

Bronchial Spasmolytics

The smooth muscles tone of bronchi is under control of parasympathetic nervous system, excitation of which results in spasm of bronchi. Sympathetic innervation of bronchi is absent. However, both α- and β_2-adrenergic receptors are located in bronchial smooth muscles. These receptors are excited by catecholamines of blood or by administered adrenoceptor agonists. Excitation of α-adrenoceptors results in spasm of bronchi, while excitation of β_2-adrenoceptors causes the bronchodilation.

Besides vegetative innervation, bronchial tone is under control of the ratio of concentration cAMP/cGMP in the smooth muscle's cells. An increase of cAMP concentration and a decrease of cGMP leads to bronchodilation.

Bronchial spasmolytics are classified as follows.

1. Adrenoceptor agonists.

1.1. Adrenoceptor agonists with direct action:

– α, β-adrenoceptor agonist: *adrenaline (epinephrine)*;

– nonselective $\beta_{1,2}$-adrenoceptor agonists: *isadrinum (isoprenaline), orciprenaline;*

– selective β_2-adrenoceptor agonists: *salbutamol (Ventolin), fenoterol (Berotec), terbutaline (Bricanyl), salmeterol, formoterol*.

1.2. Adrenoceptor agonists with indirect action (sympathomimetics): *ephedrine* and ephedrine-containing drugs (*Theophedrin, Antasthman, Solutan,* etc.).

2. M-cholinergic antagonists: *atropine, platyphyllin, ipratropium bromide (Atrovent), metacinium (metocinium iodide), troventol, oxytropium bromide, tiotropium bromide (Spiriva®), bamipine (Soventol).*

3. Myotropic antispasmodics: *theophyline, euphyllinum* (*aminophylline*).

4. α-Adrenoceptor antagonists: *phentolamine, pyrroxane, prazosin*.

5. Calcium channel blocker: *nifedipine (fenigidin, Adalat).*

Adrenoceptor Agonists

Adrenaline (epinephrine) is nonselective α- and β-adrenoceptor agonists. It should be noted that β-adrenoceptors are more sensitive to adrenaline than α-adrenoceptors. Therefore, certain doses of adrenaline do not influence α-adrenoceptors and do not cause vascular spasm and elevation of the blood pressure.

Owing to stimulation of β_1-adrenoceptors, epinephrine increases the cardiac contraction and heart rate that leads to the increase of myocardial oxygen demand. Simultaneously, adrenaline increases renin secretion by juxtaglomerular apparatus that activates the renin-angiotensin-aldosterone system and increases the vascular tone (influence of angiotensin II) and circulating blood volume.

Excitation of β_2-adrenoceptors of smooth muscles and tissue basophils results in activation of adenylate cyclase and increase of cAMP level. Owing to this, level of free calcium ions in the cells decreases and relaxation of bronchial smooth muscles develops. The release of histamine, serotonin, slow-reacting substance of anaphylaxis, that includes leukotrienes LTC_4, LTD_4 and LTE_4, and other bronchoconstrictors also decreases.

Adrenaline is administered parenterally because in case of peroral intake epinephrine is inactivated by COMT (catechol-*O*-methyltransferase) in gastrointestinal tract. Optimal mode is intramuscular because the excitation of β_2-adrenergic receptors in vessels of skeletal muscles results in vasodilatation and increase of adrenaline absorption speed. In case of subcutaneous administration, α-adrenergic receptors are mainly excited, that results in vasoconstriction and slows down the drug absorption. Intravenous and intra-arterial routes of epinephrine administration are no used due to danger of tachyarrhythmias and gangrene.

In case of intramuscular administration, bronchodilation develops in 3–7 minutes and lasts up to 30–40 minutes. Epinephrine's biotransformation occurs in all tissues of body by means of methylation and desamination. Metabolites of adrenaline exhibit β-adrenoblocking activity that is a cause fast tolerance to the drug.

Side effects are increase of blood pressure, tachycardia, elevation of minute blood volume, hyperglycemia, tremor, etc.

Adrenaline is used to interrupt an asthma attacks when other adrenomimetics are ineffective.

Ephedrine is indirect α- and β-adrenoceptor agonist (sympathomimetic). The drug stimulates noradrenaline release by sympathetic nervous terminals, inhibits mediator reuptake, and sensitizes adrenergic receptors to catecholamines.

In frequent ephedrine use, tachyphylaxis develops owing to exhaustion of noradrenaline storage in presynaptic adrenergic fibers.

In comparison with adrenaline, broncholytic activity of ephedrine is less, but duration of action is longer. Drug is administered parenterally, in inhalations, and perorally after a meal. In case of peroral intake, the effect develops in 40–60 minutes. Duration of action is up to 6 hours. At intramuscular administration, effect develops in 10–15 minutes and lasts up to 4 hours.

Ephedrine is used both to interrupt and to prevent bronchospasms.

Side effects of ephedrine are excitation of central nervous system, insomnia, increase of blood pressure, tachycardia, elevation of minute blood volume, hyperglycemia, tremor, etc. Adrenaline can cause paradoxical drowsiness in child under 5-year-old.

Isadrinum (isoprenaline) is direct β_1- and β_2-adrenoceptor agonist. Drug is administered in inhalations, sublingually, and parenterally. For interruption of bronchospasm, it is administered in inhalations. In this case, effect develops in 1–3 minutes and lasts up to 1–1.5 hours. At peroral intake, isadrinum undergoes fast degradation. Sublingual and intravenous modes of administration are used to treat atrioventricular blockage and other disturbances of heart rhythm.

Even inhalation administration of isadrinum can increase heart rate and cardiac output due to stimulation of β_1-adrenoceptors of the heart. Blood pressure is not practically changed at inhalation administration of the drug.

Salbutamol (Ventolin), fenoterol (Berotec), terbutaline (Bricanyl), salmeterol, and *formoterol* are selective β_2-adrenoceptor agonists. These drugs have no pronounced effects of β_1-adrenergic receptors stimulation, such as tachycardia, disturbances of cardiac rhythm, hypertension, and tremor.

Selective β_2-adrenoceptor agonists are administered parenterally (subcutaneously, intramuscularly, or intravenously), in inhalations, and perorally. In case of peroral intake, bioavailability of these drugs is about 50 %. At inhalations, a patient does 1–2 inspirations of the drug. At 1st inspiration, the drug reaches proximal bronchus and, through jugular vein, carried in the right ventricle and after – in pulmonary circulation. At 2nd inspiration, the drug reaches distal part of bronchus and enters the left ventricle, after that – in systemic circulation. Most of the inhaled drug "settles" in the upper sections of respiratory tract, from which it is gradually removed into the stomach, that can lead to side systemic effects as in case of peroral intake.

At parenteral administration, β-adrenomimetics reach to all part of respiratory system, where exhibit their broncholytic effect. The degree of β-adrenomimetics binding with plasma proteins is 10–25 %.

Bronchodilatation develops in 3–5 minutes after inhalations and in 20–30 minutes in case of parenteral administration. At peroral intake, the effect develops in 1 hour.

Salbutamol (Ventolin) is prescribed in aerosol for 1–2 inspiration up to 6 times a day. Powder-like form of salbutamol is administered by means of spinhaler no more than 4 times a day. In comparison with aerosol, powder-like form has some advantage. Thus, about 15 % patients can not coordinate the inhaled drug administration with act of inspiration, whereas the use of spinhaler does not require this. Insufficient efficacy of therapy with salbutamol, short period of half-life, significant prevalence of nocturnal asthma attacks were the reasons for creating of prolonged drug form salbutamol SR. Twice-daily tablet formulation of

salbutamol SR provides the stable plasma concentration of drug during a day.

Fenoterol (Berotec) has higher broncholytic activity and longer action than salbutamol. The drug is administered by 1–2 inhalations 2–3 times a day.

Terbutaline (Bricanyl) is administered by 1–2 inhalations 3–4 times a day to treat bronchial asthma.

Prolonged forms of β_2-adrenomimetics (*formoterol*, *salmoterol*, etc.) act about 12 hours. These drugs are prescribed 2 times a day that allows to use them for prevention of asthma attacks at morning.

Biotransformation of β_2-adrenomimetics occurs in different organs by COMT and MAO (monoamine oxidase). Some drugs undergo conjugation with glucuronic or sulfuric acids. The unchanged drugs and their metabolites are excreted by kidneys. At inhalations, the excretion through the lungs has an important meaning.

It should be noticed that high doses of selective β_2-adrenoceptor agonists can excite also β_1-adrenoceptors with development of tachycardia, disturbances of coronary blood circulation, heart failure, hyperglycemia, tremor, etc. Long-term use of β_2-adrenoceptor agonists is accompanied by decrease of β_2-receptors sensitivity with reduction of broncholytic effect. Such cases need to cancel β_2-adrenoceptor agonist and to prescribe of M-cholinergic antagonists, glucocorticoids and other drugs to restore β_2-adrenoceptors sensitivity.

Selective β_2-adrenoceptor agonists are used both for cessation and for prevention of asthma attacks. At acute bronchospasm, β_2-adrenomimetics are administered parenterally. Inhalant or peroral β_2-adrenomimetics are prescribed at moderate bronchospasm, for prevention of asthma attacks, and for potentiation of broncholytic action of aminophylline, chromoglycate sodium or glucocorticoids. Prolonged drugs (*salmeterol, formoterol*) are used to prevent the nocturnal asthma attacks and exercise-induced bronchoconstriction.

Presently, inhalant powder-like drug *Seretide Multidisk* is implemented to treat asthma. The drug contains salbutamol and fluticasone propionate.

M-Cholinergic Antagonists

Belladonna-containing drugs, atropine, platyphyllin, and *metacinium* were first effective drugs for treatment of asthma. These drugs are prescribed in aerosols, taken orally or administered parenterally. But short duration of action (about 1.5–2 hours), predominant influence upon the upper sections of the bronchi, increase of the sputum viscosity, and numerous side effects have become an occasion for restrict of its use in treatment of asthma. It should be noticed that atropine keeps its meaning at bronchospasm due to intoxication by cholinesterase inhibitors or M-cholinomimetics, inspiration of irritative agents, etc.

Nowadays, M-cholinergic antagonists for inhalation are used in medical practice. These drugs are *ipratropium bromide* (*atrovent*) and *troventol*. Both drugs are quaternary compounds with low solubility in lipids. Therefore, these drugs have selective influence upon M-cholinoceptors of bronchi. Also, these drugs decrease the release of allergy mediators from the basophils. Atrovent is used for inhalations in aerosol and in capsules for inhalations. Troventol is used in aerosol. Its effect develops in 20–40 minutes after inhalation and lasts up to 8 hours. At inhalation, part of the drug enters the gastrointestinal tract, but its absorption is about 6 %. The drug is metabolized in the liver and excreted with urine and, partly, – with feces. Troventol does not penetrate central nervous system.

Atrovent and troventol are used to prevent and treat bronchospasms in chronic obstructive bronchitis, acute and chronic pneumonia, and in bronchial asthma as additional drugs at therapy by β-adrenomimetics. These drugs are used to prepare respiratory tract for inhalation of antibiotics, mucolytics, glucocorticoids, and cromolyn sodium. It should be noticed that efficacy of drugs is higher in elderly patients (independently on form of bronchial

asthma). Sometimes, high efficacy of atrovent and troventol is observed at so-called "psychogenic" asthma.

These drugs are well tolerated by patients. Side effects of atrovent and troventol are dry mouth, disturbances of accomodation, increase of viscosity of sputum, etc.

Tiotropium bromide blocks simultaneously M_1-cholinergic receptors in ganglia and M_3-cholinoceptors in smooth muscles of bronchi and bronchial glands. The drug's effect develops in 1.5–2 hours and lasts up a day.

Nowadays, pharmaceutical industry produces co-formulated drugs *Berodual* (containing atrovent and fenoterol) and *Ditec* (containing cromoglycate sodium and fenoterol). The efficacy of such co-formulated drugs is higher than at the use of each components itself.

Myotropic Antispasmodic Drugs

Theophylline and *euphyllinum* (*aminophylline*) are methylxanthines which are used to treat bronchial asthma.

Despite of medicine is using these drugs more than 70 years, their mechanism of action is not clear enough. It is known that these drugs block the activity of phosphodiesterase – enzyme which catalyzes the transformation of cAMP to inactive 5-AMP. On the molecular level, stabilization of cAMP level causes the decrease of calcium entrance into the cells and reduction of bronchial tone.

Simultaneously, drugs also block adenosine receptors. Adenosine is agonist of purinergic receptors A_1 and A_2. Bronchospasm develops if the activity of A_1-receptors is more than activity of A_2-receptors. In patient with bronchial asthma the quantity of A_2-receptors is reduced. Methylxanthines restore quantity of A_2-receptors and reduce quantity of A_1-purinergic receptors, that results in bronchodilation.

Also, methylxanthines stabilize the membranes of basophils and reduce the release of allergy mediators promoting bronchospasm. But this the effect is of secondary importance at the prescribing of usual therapeutic doses of drugs.

Methylxanthines inhibit the release of cytokines stimulating inflamation (interleukins 1β, 4, and 5) and increase synthesis of interleukin 10 exhibiting anti-inflammatory action.

Besides, an influence of drugs upon the mucociliary transport and mucosal oedema is not excluded.

Methylxanthines stimulate respiratory centre, increase heart activity, decrease the blood pressure in pulmonary artery, stimulate synthesis and release of endogenous catecholamines by adrenal medulla, and improve contractability of the emaciated diaphragmatic muscle. Methylxanthines have weak diuretic activity owing to increase of kidney blood flow. These drugs stimulate central nervous system and irritate stomach mucosa.

Drugs are administered intravenously slowly or drop-by-drop, intramuscularly, orally (prior a meal) and rectally. Bioavailability of methylxanthines from gastrointestinal tract is about 90 %. The degree of binding with plasma proteins is about 50 %. These drugs easily penetrate through blood-brain and placental barriers and are excreted in mather's milk. The blood therapeutic concentrations are maintained during 4–5 hours. Drugs are administered 4–6 times per day.

Methylxanthines undergo hepatic biotransformation by means of oxidation and demethylation. It should be noticed that only 10–20 % administered dose of methylxanthine is metabolized in newborns, premature baby, and elderly patients. Metabolism of methylxanthines increases in child aged 1–10 years. Some drugs (glucocorticoids, barbiturates, rifampicin, etc.), smoking, and protein-rich meals accelerate metabolism of methylxanthines. Methylxanthine metabolites are excreted with bile. About 10 % administered dose of xanthine is excreted in unchanged form by kidneys. Clearance of methylxanthines is higher in men than in women, so, the latter have higher possibility of xanthine overdose and intoxication.

Methylxanthines are administered parenterally for interruption of asthmatic status. Wherein, ampule's content is diluted by isotonic sodium chloride solution and is heated to body temperature. It is impossible to dilute aminophylline by glucose solution because it

slows doun the hepatic metabolism of the drug and promotes its accumulation.

Also, methylxanthines are used to prevent bronchial asthma attacks.

There are prolonged forms of theophylline which are classified into two generations:

– 1st generation drugs: *Theopec, Theo-Dur, Ventax, Durofillin, Retafyllin, Theotard*;

– 2nd generation drugs: *Theo-24, Uniphyl, Phyllocontin, Euphylong*.

The 1st generation drugs are prescribed two times a day: 1/3 dose is taken at morning and 2/3 – at evening. The 2nd generation drugs are taken once a day at evening.

Methylxanthines side effects are nausea, tachycardia, tremor, headache, insomnia, etc. Due to stimulation of gastric secretion, methylxanthines can provoke exacerbation of ulcer disease in some patients.

The overdose of methylxanthines leads to intoxication. Riboxin (inosine) intravenously slowly, anticonvulsants, and diuretics are used to reduce the symptoms of intoxication. In severe cases, hempsorption or hemodialysis are preformed and sympthomatic therapy is prescribed.

α-Adrenoceptor Antagonists

Prazosin, phentolamine, and *pyrroxane* block α_1-adrenergic receptors of prealveolar sphincters and improve bronchial patency. Broncholytic activity of these drugs is significantly less than activity of β-adrenomimetics. But α-adrenoceptor antagonists can be useful in patients with tachyphylaxis to β-adrenoceptor agonists or in patients with accompanied hypertension or chronic heart failure.

Calcium channel blockers

Calcium antagonists are increasingly used in a treatment of bronchial asthma. These drugs reduce calcium entrance into smooth muscle cells of bronchi. Calcium ions participate secretion of mediators by basophiles, in processes of cellular adhesion and epithelial permeability. Calcium ions are essential for normal function of enzymes (e. g., adenylyl cyclase and guanylyl cyclase), nervous impulse transmission, and muscular contraction and relaxation. But, the role of drugs in therapy of bronchospasms is not clear enough. There is evidence about the effective use of calcium antagonists (nifedipine) to prevent bronchoconstriction in patients suffering by exercise-induced asthma.

Drugs Eliminating Oedema of Bronchial Mucous Membrane

Glucocorticoids

Glucocorticoids (*beclomethasone, budesonide, flunisolid, triamcinolone*, etc.) play an important role in a therapy of bronchial asthma. These drugs influence upon different links of asthma pathogenesis and are indispensable in severe forms of the disease.

Mechanism of glucocorticoids action at syndrome of bronchial obstruction is not clear enough. It is proved that glucocorticoids suppress exudation and limit oedema of bronchi mucous membrane. These effects arise due to the reduction of synthesis of inflammation mediators (e. g., prostaglandins), potentiation of catecholamines action owing to the increase of cAMP activity, inhibition of M-cholinergic activity owing to the decrease of cGMP activity, direct drugs influence upon smooth muscles of the bronchi, and antiallergic action of glucocorticoids. It should be noticed that glucocorticoids, first of all, inhibit hyperactivity of delayed type, and only in prolonged use – hyperactivity of immediate type.

Drugs are administered in inhalations, perorally, intramuscularly, and intravenously. Administration of drugs by

means of all routes, except inhalational, can leads to many side effects. A use of special inhalation forms (dosed aerosols) allows to avoid majority of side effects. Aerosols exhibit anti-oedema effect, prevent bronchoconstriction, and improve evacuation of thick and viscous sputum.

At inspiration of aerosol, only 10–20 % dose enters to the lungs, main amount of the drug is swallowed into the stomach. But significant systemic effects do not develop in this case. Drugs undergo hepatic biotransformation. About 70 % metabolites are excreted with the bile, and about 20 % – with urine.

A use of inhaled glucocorticoids restors the reaction of bronchi to bronchodilators and decrease the frequency of administration of the latter.

Inhaled glucocorticoids do not cause a fast effect. Therefore, these drugs used to treat chronic bronchial asthma only. Inhaled glucocorticoids are ineffective and are no used to treat acute asthma attacks. At bronchoconstriction in patients with hormonal-dependent asthma and at asthmatic status, glucocorticoids are administered parenterally or taken orally (in milder cases). Administered doses are individual and drugs are administered 2–4 times a day. Both when systemic glucocorticoids are prescribed and when inhaled forms are administered, the step approach is used. That is, high dose of drug is prescribed initially and is decreased after reach of the therapeutic effect. Considering circadian rhythm of corticosteroid release by an adrenal cortex, inhaled glucocorticoids are usually prescribed in first part of a day.

Cough and hoarseness can be observed at the used of inhaled glucocorticoids. Sometimes, paradoxical bronchoconstriction develops that can be easily prevented by prior administration of bronchodilators. Gastritis and ulcer disease are also possible. Sometimes, a rosacea appears. It is necessary to remember about possibility of candidiasis. To prevent this complication, is necessary to rinse mouth and throat. At initial symptoms of candidiasis, antifungal drugs are prescribed.

Stabilizers of Tissue Basophiles Membranes

This group includes such drugs as *sodium cromoglycate*, *nedocromil sodium*, and *ketotifen*. Drugs are used only to prevent bronchoconstriction and for systematic treatment of bronchial asthma (mainly of allergic origin). Stabilizers of tissue basophiles membranes are ineffective in case of acute bronchospasm.

These drugs inhibit phosphodiesterase and prevent the calcium ions entrance owing to blockade of opening calcium channels. Thus, drugs suppress the release of histamine and leukotrienes. Besides, these drugs increase activity of β-adrenergic receptors owing to restoration of their sensitivity to catecholamines.

There is evidence, that these drugs also block chloride channels of basophils. It is known, that transport of chloride ions into the basophiles results in hyperpolarization of membrane, which is necessary for penetration of calcium ions into the cells. The chlorine outflow from neurons leads to depolarization of nervous endings that increases the activity of vagus nerve with the following increase of bronchial tone. Therefore, blockage of chloride channels is the base of anti-inflammatory and antiallergic effects of stabilizers of tissue basophiles membranes. Drugs predominantly influence upon pathochemical stage of allergic reactions of immediate type. Besides, these drugs exhibit efficacy at allergic reactions of delayed type. Stabilizers of membranes of tissue basophiles decrease the oedema of bronchi mucous membrane and prevent (but not eliminate) bronchospasm.

Sodium cromoglycate and *nedocromil sodium* are used as solutions or powders for inhalations. Only 10 % of administered dose reaches to distal part of respiratory tract. Most of the dose “settles” on the mucous membranes of mouth and pharynx and enters the stomach during swallowing. But these drugs are not absorbed from gastrointestinal tract and are excreted with feces. Maximal effect of the inhaled drug develops in 2 hours and lasts about 4–6 hours. Drugs are administered 2–4 times a day.

Sometimes, an inhalation of powder-like forms of the drugs is accompanied by bronchoconstriction. In such case, bronchodilators are administered previously to prevent it.

Stabilizers of tissue basophiles membranes are used for treatment of atopic bronchial asthma. Pronounced effect develops in 2–8 weeks after the treatment initiation. The large advantage of therapy by these drugs is possibility to decrease or even discontinue glucocorticoids intake. These drugs are commonly prescribed together with bronchodilators and expectorants.

Anti-inflammatory activity of nedocromil sodium is in 10 times more than activity of sodium cromoglycate. Nedocromil sodium is effective in both allergic and non-allergic asthma. Maximum therapeutic activity of drugs develops in 5–7 days after initiation of treatment. Drug is prescribed 2 times a day.

There are the special forms of nedocromil-sodium and sodium cromoglycate which used to treat allergic rhinitis (*Lomusol*, *Rynacrom*) and conjunctivitis (*Opticryl*, *Tilavist*). Also, *Nalcrom* (effective medicinal form of sodium cromoglycate) is used in the treatment for alimentary allergy.

Mechanism of *ketotifen* action is similar to nedocromil sodium. Bisedes, ketotifen is able to block H_1-histaminergic receptors. Drug is administered perorally after a meal. About 90 % of administered dose of ketotifen is absorbed from gastrointestinal tract. Its degree of binding with plasma proteins is about 75 %. Therapeutic concentration in the blood is observed in 2 hours after drug intake and keeped up to 12 hours. Drug is prescribed 1–2 times a day. Ketotifen undergoes biotransformation in liver. Its metabolites are excreted with urine and bile.

Side effects are dry mouth, decrease of bronchial secretion, hoarseness, drowsiness, and increase of appetite.

Drugs Influencing Leukotriene System

Inhibitors of Leukotriene Synthesis

Leukotrienes play an important role in pathogenesis of atopic bronchial asthma. Leukotrienes are synthesized from arachidonic acid by means of enzymes, one of which is 5-lipoxygenase. This key enzyme of leukotriene synthesis is contained in tissue basophils, eosinophils, monocytes, and neutrophils.

Zileuton selectively blocks 5-lipoxygenase and affects synthesis of leukotrienes A_4, B_4, C_4, D_4 and E_4. It leads to anti-inflammatory and broncholytic effects. The drug does not influence activity of cyclooxygenase.

Zileuton is easily absorbed from gastrointestinal tract. Maximal drug concentration in the blood is observed 2–2.5 hours after oral intake. The degree of its binding with plasma proteins is 93 %. The drug is taken 4 times a day.

Zileuton is used to treat bronchial asthma. Besides, its anti-inflammatory effect may be useful at rheumatoid arthritis and ulcerative colitis. Side effects of zileuton are fever, headache, dizziness, muscular pain, dispepsy, and fatigue.

Blockers of Leukotriene Receptors

Zafirlukast (Accolate) blocks cysteinyl leukotriene (CysLT) receptors C_4, D_4, and E_4 and, thus, prevents effects of leukotrienes. Accolate eliminates bronchoconstriction, decreases vascular permeability, and inhibits bronchial secretion.

The drug is taken orally 2 times a day in 1.5–2 hours prior a meal. Its degree of binding with plasma proteins reaches 99 %. Stable therapeutic effect is observed in a week from the treatment initiation. About 90 % of taken dose is excreted by the liver. Accolate easily penetrate placenta and is excreted with mother milk. Patients who treated by zafirlukast should avoid intake of theophylline.

Zafirlukast is used in the basic treatment for atopic bronchial asthma and aspirin-, cold- and exercise-induced asthma.

Zafirlukast may be combined with glucocorticoids, β-adrenomimetics, and stabilizers of membrane of tissue basophils.

Zafirlukast should be taken regullary, even in periods which are free from asthmatic symptoms. It is aspecially necessary to adhere to the mode of administration of the drug in periods of asthma exacerbation. Even regular drug intake during a year does not result in tolerance. Discontinuation of zafirlukast does not leads to aggrevation of patient's condition.

Pranlukast and *montelukast (Singulair)* are drugs which are also reffered to the group of blockers of leukotriene receptors. Montelukast is taken 1 time a day.

Expectorant Drugs

This group includes a lot of drugs decreasing a sputum viscosity and facilitating its discharge. These drugs are used in symptomatic therapy for serious cough with little amount of viscous sputum (e. g., acute respiratory diseases, pleuritis, whooping cough). Expectorants decrease a number of infectious agents in the bronchi, improve the bronchial drainage and gaseous exchange, decrease the inflammation and irritation of nervous ending in bronchial mucosa.

Expectorant drugs are classified as follows.

1. Expectorant drugs of direct action: *root of Althaea officinalis (marsh-mallow), leaves of plantain, mucaltin, pertussinum, potassium iodide, terpin hydrate, sodium benzoate, sodium hydrocarbonate*.

2. Expectorants of reflex type of action: *grass of Thermopsis, grass of Labrador tea, root of milkwort, ipecacuanha,* etc.

3. Mucolytics: *acetylcysteine, bromhexinum, ambroxol, desoxyribonuclease, crystalline trypsin,* etc.

Expectorant Drugs of Direct Action

Most representatives of this group are agents of plant origin. It is thought that after absorption into blood, these drugs are partly secreted by bronchial glands and have the covering and anti-inflammatory action. Also, these agents increase the production of bronchial secretion.

Because the plant agents have the insufficient action upon the viscosity of sputum, these drugs are commonly combined with iodides, bromides, terpin hydrate, sodium benzoate, sodium hydrocarbonate, etc. Iodine ions, secreted by bronchial glands, increase the secretion of water and decrease the viscosity of sputum.

Mucaltin contains mix of polysaccharides obtained from grass of *Althaea officinalis*. The drug is prescribed in tablets for oral intake.

At peroral intake of small doses (about 0.25 g) of *sodium hydrocarbonate*, its expectorant effect is doubtful because the agent is neutralized by hydrochloric acid of stomach. Therefore, intake of 35 g of sodium hydrocarbonate with hot milk, honey, and 2–3 drops of iodine is more effective.

A large amount of drunk water also increases bronchial secretion.

The combination of peroral administration of expectorants with inhalation therapy is more effective. The sodium hydrocarbonate is the main component of common solution for inhalations. This agent has neutralized and loosening effects concerning acidic mucopolysaccharides and decreases its viscosity. Bromides or iodides can be also added to inhalation solutions. At steam inhalations, vegetable essential oils (e. g., anise, eucalyptus) are effective. These oils exhibit emollient and anti-inflammatory effects.

Expectorant Drugs of Reflex Action

This group includes the drugs of plant origin which contain saponins. For expectorant effect, these drugs are taken orally. Saponins irritate the mucous membrane of stomach and reflexively cause the weak stable activation of vomiting centre. The expectorant

doses of these agents are less than the threshold vomitive doses; therefore, vomiting and significant nausea do not arise. But mild nausea reflexively activates the parasympathetic nervous system that is accompanied by increasing of secretion of salivary, gastric, and bronchial glands; decreasing of viscosity of sputum, and facilitating of sputum discharge. The activity of bronchi ciliary epithelium is increased. Lysosomal enzymes, released by goblet cells of epithelium, promote the proteolysis of sputum proteins. Expectorants of reflex action improve the release of viscous slippery sputum. These drugs are used in the treatment for acute respiratory diseases with poor slippery secretion.

The high doses of these agents significantly excite the vomiting centre and cause the nausea and vomiting.

Mucolytics

Acetylcysteine (ACC), bromhexine, ambroxol (Mucosolvan, Lasolvan), Mesna, crystalline trypsin, desoxyribonuclease, crystalline chymotrypsin and other drugs are reffered to this group.

Molecules of *acetylcysteine* contain free HS-group. Due to this, the drug reduces the disulfide groups of glycoproteins. The breakage of disulfide bonds is accompanied by depolymerization of protein components of sputum that improves its discharge. Simultaneously, amount of liquid component of bronchial secretion is increased.

Unlike proteolytic enzymes (trypsin, chymotrypsin), acetylcysteine does not aggressively influence upon the epithelium and does not increase the size of defects in mucous membrane. Nowadays, acetylcysteine is one of the basic agents in the treatment for chronic bronchitis, pneumonia, and bronchiectatic disease. About 4–8 ml of 10 % acetylcysteine is used in inhalations 3–6 times a day. Inhalation, lasting 15–20 minutes, is accompanied by active coughing. After liquidation of acute symptoms, the maintenance therapy (1–2 inhalations of acetylcysteine a week) is used. Also,

acetylcysteine is administered intramuscularly or intravenously. The drug is contraindicated at bronchial asthma.

Pharmacological properties of *Mesna* are similar to acetylcysteine. The drug is administered in inhalations.

Bromhexinum and *ambroxol* increase the activity of lysosomes of epithelial goblet cells, secretion of proteolytic enzymes, and synthesis of surfactant by pulmonary tissue. Surfactant synthesized in the alveols and consists of phospholipids, proteins and polysaccharides. Surfactant provides elasticity of pulmonary tissue and promotes the discharge of sputum from pulmonary tract. Also, bromhexinum and ambroxol increase the synthesis of lysozyme and immunoglobulins G and A. Both drugs show the mild antitussive activity.

Bromhexinum is used in aerosol for inhalations and in tablets for oral intake 3–4 times a day. Its effect develops in a day, but maximum effect is observed in 5–10 days after the therapy initiation. The drug is well tolerated by patients. Ambroxol is taken orally 2–3 times a day. The drug is low toxic. Sometimes, ambroxol may be the cause of nausea and vomiting.

Antitussive Drugs

Antitussive drugs suppress cough reflex due to either inhibition of cough centre or decrease of sensitivity of nervous endings in respiratory tract.

The excessive, exhausting cough promotes irritation of mucous membranes, its hyperemia, impairs the condition of patient. In such cases, the cough attacks are not productive and are not accompanied by discharge of sputum.

The excessive inhibition of cough centre by antitussive agents is also inadmissible, because in this case the discharge of sputum is broken. Therefore, the doses of antitussive drugs should be correctly chosen. These agents are used in bronchitis, pneumonias, bronchiectatic disease.

Classification of antitussive drugs is as follows.

1. Drugs with central action, which suppress the cough centre:

– opioid analgesics: *codeine* and *ethylmorphine*;

– non-opioid antitussive drugs: *glaucine, oxeladine (Tusuprex),* and *butamirate*.

2. Drugs with peripheral action, which block the sensitive nervous endings in respiratory tract: *Libexin (prenoxdiazine).*

Codeine is alkaloid of opium. Drug exhibit moderate analgetic and expressed antitussive effects. Its duration of action is 3–4 hours. The therapeutic doses of codeine do not suppress the respiratory centre. Long-time use of codeine can cause constipations and urinary retention. Codeine is contraindicated to children under 2 years. Prolonged use of codeine can cause the development of addiction.

Ethylmorphine is obtained by chemical modification of morphine. Its antitussive activity is 1.5–2 times higher than codeine's activity.

The creation of the drugs that selectively inhibit the cough centre and do not cause addiction was an important achievement in antitussive therapy. These agents are called non-opioid antitussive drugs. Therapeutic efficacy of these drugs is about equal to codeine. But these drugs also exhibit antispasmodic action upon smooth muscles of the hollow organs. Non-opiod antitussive drugs do not cause tolerance and drug dependence.

Glaucine exhibits the moderate antitussive effect and decreases the oedema of bronchi mucous membranes. The drug is well tolerated by adults and children (over 2 years old). Sometimes, glaucine can cause the drowsiness, dizziness, and weakness.

Libexin (prenoxdiazine) is antitussive agent with peripheral action. The base of its antitussive effect is local anaesthetic action. Besides, Libexin has the bronchial antispasmodic action which is higer than antispasmodic effect of papaverine. It is supposed, that Libexin has mild inhibitory influence upon the cough centre. Libexin is taken orally 3–4 times a day. The drug is well tolerated by adults and children. Libexin does not cause drug dependence.

Chemical structure of *butamirate (Sinecod)* is similar to the structure of *oxeladine (Tusuprex)*. Besides central antitussive action, the drug exhibits expectorant, anti-inflammatory, and bronchodilating effects. Tablets, drops or sirup of Sinecod are taken orally to treat acute and chronic cough. Butamirate is component of co-formulated drug *Stoptussin*.

Analeptics

Analeptics (so-called "reviving" drugs) are drugs which directly or reflectory stimulate activity of respiratory and vasomotor centres. According to mechanism of action, analeptics are classified as follows.

1. Analeptics with central action: *caffeine*, *bemegride*, *etimizol*, and *corazole*.
2. Analeptics with reflex action: *lobeline* and *cytitonum*.
3. Analeptics with mixed mechanism of action: *cordiamine* (*nikethamide*), *camphor*, *sulfocamphocaine*, and *carbogen*.

Analeptics with reflex action cytitonum and lobeline stimulate respiratory centre due to excitation of N_n-cholinergic receptors of carotid bodies. These drugs are reffered to the group of N-cholinomimetics and their characteristics are given in the appropriate chapter. It should be noticed that these drugs practically are not used nowadays.

Depending on predominant influence upon certain parts of central nervous system, the drugs of 2nd and 3rd groups are divided into 3 groups:

– analeptics with predominant influence upon the brain cortex: *caffeine*;

– analeptics with predominant influence upon medulla oblongata: *cordiamine*, *etimizol*, *camphor*, *bemegride*, *sulfocamphocaine*, and *carbogen*;

– analeptics with predominant influence upon spinal cord: *strychnine*.

Stimulation of respiratory centre by analeptics is manifested by the increase of minute volume and frequency of respiration. This effect is most pronounced at respiratory depression. It should be noticed that analeptic effect is unstable and short-term. But analeptics give time gain which is aspecially important for liquidation of the cause of the disruption of vital functions.

The analeptics with moderate but prolonged effect are most valuable. Such analeptics are etimizol, cordiamine, camphor, and sulfocamphocain. Practical implementation of etimizol led to discontinuation of bemegride's use.

At repeated respiratory depression (that is after administration of analeptic), repeated administration of analeptics is dangerous, because it can provoke either exhaustion of respiratory centre or convulsions. Clonic convulsions are associated with predominant excitation of the brain. Administration of corazol, bemegride, cordiamine, and camphor can provoke clonic convulsions. Tetanic seizures can occur after strychnine administration which excites mainly spinal cord. High doses of the drugs predominantly influencing brain can provoke clonic-tonic convulsions.

Stimulation by analeptics of vasomotor centre and sympathetic innervation of the heart results in certain increase of vascular tone and blood pressure. In generally, Blood supply is improving. This effect is marked againt the background of the lowered blood pressure. Except camphor and caffeine, analeptics have no direct influence upon the heart.

Pharmacological characteristic of c*affeine* is given in the appropriate chapter ("Psychostimulants").

Cordiamine (*nikethamide*) is 25 % solution of diethylamide of nicotinic acid. The drug is readily absorbed after oral intake, undergoes hepatic metabolism with partial formation of nicotinamide that does not influence pharmacological properties of the drug. Inactive metabolits of cordiamine are excreted by kidneys. Cordiamine excites respiratory and vasomotor centres by means of both direct stimulation of centres and reflex action (influence upon carotid artery chemoreceptors). Cordiamine increases peripheral

vascular resistance and blood pressure, stimulates frequency and depth of respiration. The drug inhibits $GABA_A$-receptors in the medulla oblongata. Cordiamine insiglificantly influences heart rate and oxygen demand of myocardium and does not have arrhythmogenic properties. It should be noticed that cordiamine exhibits convulsive activity and increases oxygen demand of brain. At central genesis collapse, cordiamine's action is more reliable than action of caffeine. Cordiamine is also used to treat moderate hypotension in elderly persons and infectious patients. The drug is used to eliminate asphyxia during surgery and in postsurgical period. The ability of cordiamine to increase general tone of central nervous system and to reduce asthenic phenomena is useful in asthenic patients.

Etimizol exhibits stable stimulative effect upon respiratory centre. Its stimulative influence upon vasomotor centre is weak. Besides analeptic properties, etimizol stimulates pituitary-adrenal system; due to this the drug is able to reduce steroid drugs withdrawal symptoms. Etimizol exhibits moderate antiallergic effect that is used in the treatment for bronchial asthma. The drug inhibits the brain cortex and may be used as sedative agent at alarm states. Simultaneously, etimizol exhibits certain nootropic properties (activates protein synthesis in the brain, increases energy exchange, and improves long-term memory.

Camphor is terpenoid which obtained from camphor laurel (*Cinnamomum camphora*) or great basil (*Ocimum basilicum*). Synthetic camphor produced by processing of turpentine. Administered subcutaneously, camphor reflectory stimulates respiration and increases vascular tone. In high doses, camphor directly stimulates vital centres of medulla oblongata. The drug has broad therapeutic window. Camphor increases the contractability of the heart, improves coronary blood flow and microcirculation, increases the resistance of heart to arrhythmogenic factors and toxic doses of cardiac glucosides. The drug stimulates inrerferon synthesis and exhibits expectorant effect. At topical application, camphor exhibits irritative and antiseptic effects. Camphor is used to treat

acute and chronic heart failure and collapse. Also, the drug is used to reduce respiratory depression at pneumonia, infectious diseases, intoxication by opioid analgesics and hypnotics. Toxic doses of camphor provoke convulsions.

Sulfocamphocaine is complex drug of camphorsulfonic acid and novocaine. The drug is water-soluble; therefore, it is administered both subcutaneously and intravenously. Indications for use of sulfocamphocaine are identical to camphor indications.

Both camphor and sulfocamphocaine can cause allergic reactions.

Bemegride (Megimide) is analeptic for intravenous administration. The drug is characterized by low degree of binding with plasma proteins and excreted with urine in unchanged form. Due to stimulation of $GABA_A$-receptors, bemegride stimulates the central nervous system, activates vital centres of medulla oblongata (first of all – respiratory centre).

Bemegride is used in the treatment for acute poisoning by hypnotics, opioid analgesics, general anaesthetics, ethyl alcohol, etc. Overdose of bemegride can provoke muscle twitching and convulsions. Bemegride is contraindicated at epilepsy and psychomotor excitement.

Carbogen is mixture of carbon dioxide and oxygen in ratio 5 : 95 volume percents. Inspiration of carbogen increases the volume of respiration in 5–8 times. Accumulation of hydrogen ions and reduction of pH in the respiratory centre irritates the chemoreceptors located in the medulla oblongate near respiratory centre. It leads to stimulation of respiration. Reflex stimulation of respiratory centre from carotid bodies is also important. Effect of carbogen develops during 5–6 minutes. Also, carbogen inspiration improves general and cerebral blood circulation.

Strychnine is alkaloid of the seeds of strychnine tree *(Strychnos nux-vomica).* The drug is readily absorbed from the gastrointestinal tract, undergoes hepatic biotransformation, and excreted with the urine. Strychnine is accumulated in the human body. The drug selectively activates the neurons of spinal cord,

facilitates the transmission in the synapses, increases the reflex activity of central nervous system, suppresses the postsynaptic inhibition mediated by glycine. Strychnine stimulates vasomotor and respiratory centres, littly activates the cortex, improves visual functions. The drug increases blood pressure, coronary circulation, and tone of both smooth and skeletal muscles and activates taste and scent. Strychnine is used to treat arterial hypotension, fast fatigability, paralysis, paresis, gastrointestinal atoly, and functional visual impairment.

Drugs Used to Treat Pulmonary Oedema

Pulmonary oedema is one of the reasons of acute respiratory insufficiency and develops at different diseases of cardiovascular system, damage of the lungs by chemicals, renal and hepatic failure.

A choice of the drugs depends on the degree of pulmonary oedema and level of blood pressure.

The drugs decreasing blood pressure are used to reduce the oedema against the background of the hypertension. With this end in view, ganglionic blockers (*hygronium*, *pentaminum*, *benzohexonium*), vasodilators of myotropic action (*sodium nitroprusside*, *nitroglycerin*), and α-adrenoblockering drugs (*phentolamine* or small doses of *aminazine*) are used. The mentioned drugs decrease the blood pressure and reduce venous return to the heart, that promotes cardiac unloading and improves its work. In result, blood pressure in pulmonary circulation is decreased and output of transudate into the alveoli is reduced.

Potent diuretics (*furosemide*, *etacrynic acid*) decrease the blood volume and blood pressure that also promotes the reduction of pulmonary oedema.

Sometimes, opioid analgesics (*morphine*, *fentanyl* or its combination with *droperidol – Thalamonal*) are used in the treatment for pulmonary oedema. The drugs relax peripheral arteries and veins and reduce cardiac preload and afterload. The use of opioid analgesics is accompanied by the decrease of blood pressure in

pulmonary circulation, reduction of dyspnea and elimination of cough.

At pulmonary oedema against the background of the arterial hypotension, the drugs for normalization of blood pressure are used (*phenylephrine*, *ephedrine*). Dehydrating drugs and diuretics are also used with caution in this case.

At pulmonary oedema, foam accumulates in the lumen of alveoli and violates the gas exchange. The antifoam agents (*ethyl alcohol*, *anti-fomosilane*) are used to inhibit the foaming. The antifoam agents decrease the superficial tension of foam bubbles; therefore, foam is transformed to liquid which takes up significantly less volume in the alveoli. Alcohol vapors with oxygen are inhaled by means of nasal cateter or mask. Alcoholic solution of anti-fomosilane with oxygen is used in aerosol for inhalation. Unlike ethyl alcohol, anti-fomosilane does not irritate mucous membranes of respiratory tract. Its effect develops faster.

Glucocorticoids (*prednisolone*, *dexamethasone*) are used to treat pulmonary oedema owing to their prominent anti-inflammatory and anti-oedema effect.

O*xygen* is inhaled in all cases of the pulmonary oedema.

Sometimes, cardiac glycosides with fast onset of action (*strophanthin*, *corglycon*) are used to treat pulmonary oedema against background of the heart failure.

Interstitial pulmonary oedema with multiple atelectasis and severe respiratory failure develops at infant respiratory distress syndrome developing due to the insufficiency of pulmonary surfactant production. Artificial pulmonary ventilation and administration of *colfosceril palmitate* (*Exosurf*) is used in such cases. Colfosceril is administered intratracheally no more than two times. The drug reduces superficial tension of pulmonary fluid and maintains elasticity of alveoli. Sometimes, *Alveofakt* is also used with this end in view. It is highly purified surfactant obtained from the lungs of cattle.

Table 1 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Codeini phosphas	Orally 0.01–0.03 g 1–3 times a day	Powders
Libexinum	Orally 0.1–0.2 g 3–4 times a day	Tablets 0.1 g
Acetylcysteinum	Orally 0.2 g 3 times a day; intramuscularly 0.1–0.2 g 2–3 times a day	Tablets 0.2 g; ampoules 2 ml of 10 % solution
Bromhexinum	Orally 0.008 g 3–4 times a daily	Tablets 0.008 g
Euphyllinum	Orally 0.25 g 2–3 times a day; intramuscularly 0.24–0.36 g 1–3 times a day; intravenously slowly or drop-by-drop (in 200–400 ml of 0.9 % solution of NaCl) 0.12–0.24 g	Tablets 0.25 g; ampoules 5 ml of 2 % solution
Cromolynum-natrium	For inhalation: 1 capsule 4 times a day	Capsules 0.02 g
Adrenalini hydrochloridum	Subcutaneously or intramuscularly (sometimes intravenously) 0.000 3–0.000 7 g	Ampoules 1 ml of 0.1 % solution
Salbutamolum	1–2 inhalations of aerosol 2–3 times a day to prevent bronchospasm or 2 inhalations to interrupt acute bronchospasm	Aerosol 10 ml
Furosemidum	Intramuscularly or intravenously 0.02 g	Ampoules 2 ml of 1 % solution
Hygronium	Intravenously drop-by-drop 0.04–0.1 g (as 0.1 % solution in isotonic sodium chloride solution)	Ampoules 0.1 g of powder for injection

Step 1. Tasks for Self-Control
Drugs Influencing Respiratory System

1. Spasm of smooth muscle of bronchi developed in the patient. Usage of activators of what membrane cytoreceptors is physiologically valid to decrease attack?

A. α-Adrenoreceptors.

B. α- and β-adrenoreceptors.

C. β-adrenoreceptors.

D. H-cholinoreceptors.

E. M-cholinoreceptors.

2. A 13-year-old girl with history of asthma complained of cough, dyspnea, and wheezing. Her symptoms became so severe that her parents brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42/min, pulse rate was 110 beats per minute, and blood pressure was 130/70 mm Hg. Choose from the following list the most appropriate drug to reverse the bronchoconstriction rapidly.

A. Salbutamol.

B. Ipratropium.

C. Methylprednisolone.

D. Beclomethasone.

E. Cromolyn sodium.

3. A 45-year-old woman suffers from allergic seasonal coryza caused by the ambrosia blossoming. What drug from the stabilizer of the adipose cells group can be used for prevention of this disease?

A. Dimedrol.

B. Tavegyl.

C. Diazolinum.

D. Ketotifen.

E. Phencarol.

4. Which of the following β-adrenoceptor agonists has such a slow onset of action that it is not indicated for the relief of acute asthma symptoms?

A. Isoproterenol.

B. Albuterol.

C. Epinephrine.

D. Terbutaline.

E. Salmeterol.

5. A patient with bronchial asthma was treated by euphyllinum, after that the condition of patient was improved. What mechanism of action has this drug?

A. Prevention of histamine discharge from basophils.

B. Blockade of phosphodiesterase.

C. Activation of Na, K-ATPase.

D. Blockade of M-cholinoreceptors.

E. Activation of adenylyl cyclase (adenyl cyclase).

6. A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parents brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42/min, pulse rate was 110 beats per minute, and blood pressure was 132/65 mm Hg. What drug is contraindicated in this patient?

A. Inhaled cromolyn sodium.

B. Inhaled beclomethasone.

C. Inhaled ipratropium.

D. Inhaled albuterol.

E. Intravenous propranolol.

7. A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parent brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42/min, pulse rate was 110 beats per minute, and blood pressure was 132/65 mm Hg. What is the most appropriate drug to rapidly reverse bronchoconstriction?

A. Intravenous propranolol.

B. Inhaled albuterol.

C. Inhaled ipratropium.

D. Inhaled cromolyn sodium.

E. Inhaled beclomethasone.

8. A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parent brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42/min, pulse rate was 110 beats per minute, and blood pressure was 132/65 mm Hg. Indicate the drug, which is likely to be ineffective in this patient.

A. Intravenously prednisolone.

B. Inhaled beclomethasone.

C. Inhaled ipratropium.

D. Inhaled albuterol.

E. Inhaled cromolyn sodium.

9. Ethyl alcohol was introduced to patient with acute pulmonary oedema. What action of ethyl alcohol was used in this case?

A. Ethyl alcohol decreases the permeability of lung's vessels.

B. Ethyl alcohol decreases the superficial tension of foam and transforms it to the fluid.

C. Analgesic action.

D. Ethyl alcohol increases the rate of metabolism into the body.

E. Hypnotic action.

10. A patient with bronchial asthma attack has a concomitant disease – angina pectoris. What bronchodilator should be prescribed in this case?

A. Noradrenaline hydrotartrate.

B. Adrenaline.

C. Salbutamol.

D. Atropine sulfate.

E. Isadrinum.

11. Chronic bronchitis is diagnosed. A patient is treated with mucolytic – a drug, which stimulates formation of surfactant,

improves rheological properties of sputum, reduces its viscosity. What is this drug?

A. Panadol.

B. Papaverine hydrochloride.

C. Libexinum (prenoxdiazine).

D. Ambroxol.

E. Codeine.

12. Bronchospasm has developed in patient using β-adrenoblockers during long time. Choose the most rational drug group for interruption of bronchospasm in this patient.

A. Cholinesterase inhibitors.

B. β-adrenomimetics.

C. Adrenomimetics with indirect action.

D. M-cholinomimetics.

E. Myotropic spasmolytics.

13. A patient with asthmatic status is delivered to urgent unit. The patient has been suffering from bronchial asthma for 12 years. Earlier attacks were reduced by salbutamol but now this drug is ineffective. What drug should be administered to patient first?

A. Prednisolone.

B. Acyclovir.

C. Oxytocin.

D. Famotidine.

E. Bisacodyl.

14. A patient with purulent bronchitis is delivered to the pulmonary department. For depression of sputum and simplification of its release the doctor prescribes to him drug A. Indicate this drug.

A. Morphine.

B. Tincture of valerian.

C. Cholosasum.

D. Acetylcysteine.

E. Prednisolone.

15. A patient with acute laryngotracheitis suffers from dry cough. Prescribe antitussive drug for this patient.

A. Morphine.

B. Glaucine.
C. Acetylcysteine.
D. Mucaltin.
E. Ambroxol.

16. A patient suffering from chronic bronchitis takes synthetic mucolytic drug that facilitates the sputum thinning. What drug is it?

A. Acetylcysteine.
B. Enalapril.
C. Heparin.
D. Diazepam.
E. Furosemide.

DRUGS INFLUENCING CARDIOVASCULAR SYSTEM

There are many drugs influencing cardiovascular system. Depending on their clinical use, these drugs are classified as follows.

1. Cardiotonic drugs.
2. Antihypertensive drugs.
3. Hypertensive drugs.
4. Antiarrhythmic drugs.
5. Drugs which used to treat ischaemic heart disease.
6. Hypolipidemic (lipid-lowering) drugs.
7. Drugs improving cerebral circulation.
8. Venotropic drugs.

CARDIOTONIC DRUGS

Cardiotonic drugs are drugs which increase contraction of myocardium and normalize the functions of heart. Cardiotonics are divided into cardiac glycosides and non-glycoside cardiotonics.

Cardiac Glycosides

Cardiac glycosides are nitrogen-free compounds with cardiotonic activity. Cardiac glycosides are contained in such plants as foxglove, lily of the valley, spring adonis, strophanthus, etc. It is known 15 species containing cardiac glycosides and used in medicine.

Presently, the main and most studied cardiac glycosides are:

– *digitoxin* – main glycoside of leaves of foxglove (*Digitalis purpurea*);

– *digoxin* and *celanidum* – glycosides of leaves of woolly foxglove *(Digitalis lanata)*;

– *strophanthin* – glycoside of seeds of *Strophanthus kombe*;

– *corglycon* – novogalenic drug derived from the leaves of lily of the valley (*Convallaria majalis*);

– *infusion of Adonis herb (pheasant's eye, Adonis vernalis*).

The glycoside content of plants varies greatly and depends on conditions of growth, drying methods, and other factors. Considering this, drugs of cardiac glycosides undergo biological standardization. The main object of study are frogs; sometimes, cats are used. The base for standardization of glycosides is their ability to cause cardiac arrest in systole (in frogs) or in diastole (in cats). The activity of investigated drug is compared to activity of standard and expressed in "frog" action units or "feline" action units. Thus, 1 g of digitoxin contains 8 000–10 000 "frog" action units (or 1 911–2 271 "feline" action units); 1 g of sthrophanthin – 43 000–58 000 "frog" action units (or 5 800–7 100 "feline" action units).

Cardiac glycosides influence cardiovascular, urinary, and nervous systems. Respectively, effects of cardiac glycosides are divided into cardiac and extracardial ones.

There are the following cardiac effects of cardiac glycosides:

1. Positive inotropic effect. Cardiac glycosides increase and shorten systole, increase stroke volume and cardiac output, and decrease the amount of residual blood in the cavity of the heart.

2. Positive tonotropic effect. Cardiac glycosides increase the tone of myocardium and decrease the size of enlarged heart. It promotes more complete expulsion of blood from the ventricles.

3. Negative chronotropic effect. Cardiac glycosides decrease heart rate and prolong diastole. As a result, blood supply to the heart improves.

4. Negative dromotropic effect. Cardiac glycosides decrease the impulse conduction through conductive heart system, especially through atrioventricular node.

5. Positive bathmotropic effect. Cardiac glycosides increase the excitability of myocardium and may promote the ventricular tachyarrhythmias.

The first three effects are the base of therapeutic action of cardiac glycosides. The fourth and the fifth effects are undesirable effects, which develop predominantly in case of glycosides overdose.

Cardiac glycosides interact with membrane Na^+, K^+-ATPase of cardiac histiocytes. Owing to this interaction, the partial blockage of ATPase activity develops. It results in increase of intracellular Na^+ ions concentration and simultaneous reduction of K^+ concentration. This change in intracellular ions balance causes the increase of Ca^{2+} ions concentration in cardiac histiocytes. The increase of free calcium concentration in the cardiac histiocytes causes the reduction of inhibitory influence of troponin upon the contractile proteins of myocardium that leads to increase of cardiac contractility. This phenomenon is called positive inotropic effect.

Cardiac glycosides form the complexes with phospholipids, proteins, and carbohydrates of the membranes of cardiac histiocytes and endothelial cells, that leads to the increase of permeability of membranes for calcium and elevation of intracellular calcium concentration.

Positive inotropic effect develops if inhibition of Na^+, K^+-ATPase equals approximately 35 %. If enzyme inhibition is less, cardiotonic effect does not develop. Toxic effects develop if enzyme inhibition equals or is more than 60 %.

Positive inotropic effect of cardiac glycosides is manifested by the increase of rate of tension development in myocardium and speed of cardiac muscle contraction, elevation of stroke volume. All systole phases are shortened. Amount of residual blood in the ventricles cavities is decreased. The following changes are observed on ECG: the increased wave R, narrowed complex QRS, decreased ST segment below the isoelectric line, and flattened or inverted T wave.

The energy of ATP is more productively used at the therapy with cardiac glycosides. An elevation of Ca^{2+} ions in diastole promotes the maintaining of myocardium tone, that is positive tonotripic effect is observed.

Prolongation of diastole and decrease of heart rate (negative chronotropic effect) is the result of increased vagal influence upon heart. Increase of cardiac contraction force is accompanied by enhance of stroke volume and excitation of baroreceptors of aortic arch and carotid glomeruli. Excitation carries out to vagus centre.

Increase of vagal tone results in decrease of excitability and automatism of sinus node and decrease of heart rate. On ECG, prolongation of interval PP is registered. Negative chronotropic effect is accompanied by the reduction of myocardium oxygen demand and improvement of metabolism in the heart during diastole that promotes the restoration of the heart energy resources, normalizes the activity of ionic channels which participate in transport of Ca^{2+} ions from the cytoplasm into extracellular space, mytochondies, and sarcoplasmic reticulum.

During treatment by cardiac glycosides, the conductibility through atrioventricular node slows down (negative dromotropic effect). Mainly, it is the result of increased vagal tone. Negative dromotropic effect is most typical for digitalis drugs. At long-time therapy by cardiac glycosides, the changes of electrolyte balance become the main cause of slowdown of impulces conduction. On ECG, prolongation of interval P–Q is observed.

Positive bathmotropic effect is ability of toxic doses of cardiac glycosides to increase excitability of myocardium which results in geterotopic focus of excitation. It is the result of significant electrolyte change in cells which develop in toxic doses (elevation of Ca^{2+} ions concentration and reduction of K^{+} ions concentration into cardiac histiocytes). Wherein, on ECG, extrasystoles are registered.

Besides cardiac effects, cardiac glycosides also have several extracardial effects. At heart failure, myocardium doesn't fulfil pump function that leads to the decrease of cardiac output and phlebostasis. Administration of cardiac glycosides increases cardiac output and decreases venous blood pressure. Blood volume in veins and hepatic portal system is decreased. Blood pressure is normalized. Owing to the increase of stroke volume and cardiac output, some elevation of blood pressure is obcerved in patients with hypotension. General blood flow and cerebral blood circulation are improved. The oxygen deficiency, blood concentration of carbon dioxide, excitability of respiratory and vasomotor centres, and dyspnea are decreased.

Diuresis increases owing to rise of blood flow and enhancement of glomerular filtration. Additionally, cardiac glycosides have direct

influence upon renal tubules: drugs block K^+, Na^+-ATPase and decrease reabsorbtion of sodium and water. Administration of cardiac glycosides results in reduction of oedemas. Cardiac glycosides have sedative effect in central nervous system.

Cardiac glycosides stimulate smooth muscles of inner organs and that leads to increase of intestinal peristalsis, increase of tone of bladder, bronchi, and uterus.

There are the following therapeutic indications for cardiac glycosides.

1. Treatment of chronic systolic heart failure.
2. Supraventricular tachyarrhythmias (digitalis drugs are preferable).
3. Prevention of heart failure.
4. Acute heart failure (strophanthin, corglycon). But in recent years, their use in acute heart failure is almost stopped owing to the introduction in medicine the safer drugs (dobutamine, dopamine, amrinone, etc.).
5. In ophthalmology, cardiac glycosides (e. g., *Digophton*) are used to treat asthenopia, presbyopia, eye pain at the migraine attack, and eye fatigue in cases of violation of blood circulation, long stay in front of the TV or sewing.

Molecule of cardiac glycosides consists of two parts: sugary part (glycone) and nonsugary one (aglycone). Glycone influence drugs pharmacokinetics: solubility, ability to penetrate through biological membranes, binding with plasma proteins, cumulation, etc. Aglycone influence cardiotropic properties of drugs. Aglycone consists of steroid part and lactone ring. Dependently of quantity of ketone and alcogol groups in glycone structure, cardiac glycoside may be polar or nonpolar. Polar glycosides are strophanthin and corglycon; relatively polar drugs are digoxin and celanidum; nonpolar glycoside is digitoxin. Polar glycosides are poorly absorbed in gastrointestinal tract, don't undergo biotransformation, and are excreted with urine. Nonpolar glycosides are well absorbed in intestine, bind with plasma proteins, undergo hepatic biotransformation, and are excreted

predominantly through intestine. Nonpolar glycosides have high ability to cumulation.

According to pharmacokinetics, cardiac glycosides are divided into three groups:

– drugs with fast onset of effect and short duration of action which are characterized by low ability to cumulation: *strophanthin* and *corglycon*;

– agents with moderate speed of effect development and intermediate duration which are characterized by reasonable degree of cumulation: *digoxin* and *celanidum*;

– glycosides with slow onset of effect and long duration of action which are characterized by high degree of cumulation: *digitoxin*.

Drugs of the first group (*strophanthin* and *corglycon*) predominantly are used in acute heart failure. These drugs are administered intravenously slowly. Prior administration, solution of glycosides is diluted in 10–20 ml of isotonic sodium chloride solution or isotonic glucose solution. Fast intravenous administration can lead to vascular spasm and increase of preload and afterload on the heart. Strophanthin effect develops in 5–10 minutes after administration and reaches maximum in 30–90 minutes. Approximately 85–90 % of administered dose is eliminated during the first day.

Drugs of the second group (*digoxin* and *celanidum*) occupy an intermediate position. These drugs are administered both intravenously and perorally in acute and chronic heart failure. Drugs effects develop in 0.5–2 hours after intravenous administration. Maximum effect develops in 1–5 hours. Drugs are completely excreted in 2–7 days.

Digitoxin is used perorally or rectally in chronic heart failure. In case of peroral use, onset of drug action is in 2 hours and maximum effect develops in 12 hours. Only 7–10 % of administered dose is excreted during the first day after administration. Digitoxin is completely excreted from the body in 2–3 weeks.

Infusion of Adonis herb is preparation of perennial herb pheasant's eye *(Adonis vernalis)*. Properties of Adonis glycosides are similar to properties of digitalis glycosides but are less effective. Also, Adonis glycosides exhibit weak diuretic effect. In comparison with digitalis glycosides, duration of action of Adonis glycosides is less; therefore, danger of cumulation is practically excluded. At oral intake, the degree of glycosides absorption is enough for therapeutic effect. Infusion of Adonis herb is used in the treatment for slight forms of chronic heart failure, neurosis, and vegetative-vascular dystonia. Adonis herb is component of Bechterew's mixture, Cardiovalen, and Adonis-bromine.

Cardiac glycosides are dosed according to certain rules. First of all, it is necessary to take into account the degree of drug's daily excretion. The coefficient of daily excretion characterizes the daily excretion of cardiac glycosides from the patient's body. This is percentage ratio of dose which was introduced into the body during the day to quantity of glycoside, which was excreted from the body during day. For example, coefficient of daily excretion of digitoxin equals 7–10 %, for strophanthin – 40–50 %.

The treatment of chronic heart failure is carried out in two phases: phase of initial digitalization and supporting phase. During the initial digitalization the full effective dose of glycoside is received in organism. The realization of phase of saturation is crucial task, as the sensitivity of the patients to glycosides is individual, and the effective dozes of drugs are close to toxic. This phase may be carried out with different velocity. The moderate (for 3 days) and slow (for 8 days) types of initial digitalization are most commonly used in practice. Fast type of digitalization (during 1 day in organism of patient the full effective dose is taken) creates the biggest threat of intoxication. Fast digitalization is fulfilled only for inpatients and under ECG control.

The scheme of moderate digitalization:

– first day: 1/2 of full effective dose (divided in 3–4 intakes) is taken by patient;

– second day: patient takes 1/4 of full effective dose (divided in 2 intakes) and amount of the drug which eliminated during 1st day (that is, coefficient of elimination for dose which patient took in 1st day;

– third day: patient takes 1/4 part of full effective dose (divided in 2 intakes) and amount of the drug which was eliminated for two days.

In the second stage (supporting phase), patient takes the supportive dose. The calculation of supportive dose is performed according to ratio: supportive dose = dose of saturation (full effective dose) · coefficient of daily excretion.

Daily supportive dose is not divided in several intakes.

Symptoms and treatment of glycosides overdose

In glycoside overdose, disturbances of heart rate observed in 90–95 % of patients. Ventricular arrhythmias (extrasystoles, paroxysmal ventricular tachycardia, and ventricular fibrillation) are most common among them. The cause of ventricular arrhythmias is decrease of potassium concentration and simultaneous increase of calcium ions concentration in cardiac histiocytes. Also, complete or partial atrioventricular blocks can develop.

Less dangerous complications include nausea, vomiting, epigastric pain, xanthopsia (seeing of objects in yellow or green colour), "rings" and "balls" before eyes, psychical disturbances (excitement and hallucinations), allergic reactions, and headache.

At appearance of overdose symptoms, the cardiac glycosides therapy is stopped. Non-glycoside cardiotonic (*dopamine* or *dobutamine*) should be prescribed.

Drugs binding glycosides and reducing their blood circulation should be prescribed. They are agents decreasing glycoside absorption in gastrointestinal tract: *tannin*, *cholestyramine*, *charcoal*, *laxative* drugs. These drugs are prescribed independently of glycoside administration mode because cardiac glycosides undergo enterohepatic circulation. Drugs binding glycosides in the blood are *unithiol* and *antibodies or digoxin*

immune Fab (Digibind). Unithiol contains sulfhydryl groups in molecules, therefore binds with cardiac glycosides and restores the activity of myocardial ATPase.

Potassium- and magnesium-containing drugs, such as *potassium chloride, Asparkamum, Panangin, polarized mixture (potassium chloride, insulin, and glucose), magnesium sulfate,* and *Trilon B* are used for treatment of glycoside intoxication. Potassium and magnesium slow down the impulse conduction, therefore they are not prescribed to patients with bradycardia and atrioventricular blockage. Intravenous administration of potassium-containing drugs should be fulfilled under control of ECG.

For treatment of ventricular tachyarrhythmias, *lidocaine* and *dipheninum* are used. In some cases, atrioventricular blockage may be reduced by administration of *atropine*.

Non-Glycoside Cardiotonics

Cardiac glycosides are highly effective drugs to treat heart failure. But their use is restricted by narrow therapeutic index, significant amount of side effects and contraindications. Therefore, synthetic non-steroid drugs with cardiotonic activity were introduced in medicine.

According to mechanism of action, non-glycoside cardiotonics are classified as follows:

1. Drugs stimulating β_1-adrenoceptors: *dopamine* and *dobutamine*.

2. Phosphodiesterase inhibitors: *amrinone, milrinone,* and *sulmazol*.

3. Drugs with different mechanisms of action: *levosimendan* and *vesnarinone*.

Dopamine is noradrenaline precursor. In average therapeutic doses, dopamine stimulates dopaminergic receptors and β_1-adrenergic receptors of heart. It results in increase of cardiac contraction force. Owing to excitation of dopaminergic receptors of smooth muscles of vessels, drug dilates renal and mesenteric vessels.

In high doses, dopamine can also excite α-adrenoceptors. Dopamine is used in severe cardiovascular insufficiency, shock, severe arterial hypotension.

Dobutamine selectively excites β_1-adrenoceptors. Drug stimulates heart work without influence upon the vessels. Dobutamine is used in acute heart failure.

Both dopamine and dobutamine are administered intravenously drop-by-drop.

Recently, cardiotonic drugs with favourable influence upon coronary circulation were approved in medical practice. *Amrinone* and *milrinone* are among them. Drugs inhibit phosphodiesterase activity and promote accumulation of cAMP in myocardium. It leads to the increase of intracellular calcium concentration, inactivation of adenosine (A_1) receptors, and cardiotonic effect.

Amrinone is administered perorally or intravenously. The drug is used in the treatment for heart failure resistant to therapy with cardiac glycosides. Duration of action is 4–7 hours. Amrinone side effects are thrombocytopenia, dyspepsia, hypotension, arrhythmias, disturbances of renal function, etc.

Cardiotonic activity of milrinone is 20 times more than amrinone. Drug is administered intravenously. Duration of action is 48–72 hours. Milrinone is used for short-term therapy of acute heart failure.

Sulmazol inhibits phosphodiesterase activity and blocks A_1 adenosine receptors of heart. It results in cardiotonic effect. Furthermore, drug increases activity of microfibrillar ATPase.

Levosimendan binds with troponin C that leads to the increase of sensitivity of the cardiac myofibrils to calcium ions. The drug increases the force of cardiac contractions without elevation of myocardial oxygen demand. Besides, levosimendan causes vasodilation, increases coronary circulation, and reduces peripheral vascular resistance; therefore, the drug has positive effect on the heart at acute heart failure. The drug is administered intravenously drop-by-drop. Duration of levosimendan's action is 6–24 hours.

Table 2 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Digitoxinum	Orally 0.000 1 g once a day; for rectal use 0.000 15 g once a day	Tablets 0.000 1 g; suppositories 0.000 15 g
Digoxinum	Orally 0.000 125–0.000 25 g once a day; intravenously slowly 0.000 125–0.000 25 g with 10–20 ml of isotonic sodium chloride solution once daily	Tablets 0.000 25 g; ampoules 1 ml of 0.025 % solution
Celanidum	Orally 0.000 25 g 3 times a day; intravenously slowly 0.000 2 g with 10–20 ml of isotonic sodium chloride solution once a day	Tablets 0.000 25 g; ampoules 1 ml of 0.02 % solution
Strophantinum	Intravenously slowly 0.000 25 g with 10–20 ml of isotonic sodium chloride solution once a day	Ampoules 1 ml of 0.05 % solution
Unithiolum	Intramuscularly 0.25 g	Ampoules 5 ml of 5 % solution
"Asparcamum" or "Pananginum"	Orally 1–2 tablets 3 times a day	Tablets containing magnesium asparaginate and potassium asparaginate
Lidocainum	Intravenously slowly 0.05–0.1 g; intravenously drop-by-drop 0.05–0.1 g with 100 ml of isotonic sodium chloride solution	Ampoules 2 ml of 10 % solution; 2 or 10 ml of 2 % solution
Dipheninum	Orally 0.117 g 1–3 times a day	Tablets 0.117 g

Step 1. Tasks for Self-Control
Cardiotonic Drugs

1. A patient with chronic heart failure being treated by digitalis drugs developed the symptoms, which confirmed the beginning of cardiac glycosides toxic activity. What drug should be administered to reduce the negative effect of cardiac glycosides?

A. Atropine sulfate.

B. Sodium chloride.

C. Potassium chloride.

D. Dipiroxime.

E. Caffeine sodium benzoate.

2. Patient complains of weakness, dyspnea, and low extremities oedema. Diagnosis: chronic cardiac insufficiency. What medicine should be prescribed first?

A. Digoxin.

B. Raunatine.

C. Propranolol.

D. Caffeine.

E. Papaverine.

3. Point out a statement which most directly describes the mechanism of action of digitalis drugs?

A. Decrease of calcium release from the sarcoplasmic reticulum.

B. Decrease intracellular concentration of sodium ions.

C. Increase intracellular level of ATP.

D. Stimulation of production of cAMP.

E. Inhibition of Na^+, K^+-ATPase.

4. Point out a drug which is not used to treat overdose of cardiac glycosides:

A. Preparations of anti-digoxin FAB fragments.

B. Polarased mixture.

C. Quinidine.

D. Dipheninum (phenytoin).

E. Lidocaine.

5. Which of the following aggravates a digitalis-induced arrhythmia?

A. Decrease of concentration of serum angiotensin II.

B. Decrease level of sodium in the blood.

C. Slowdown of heart rate by propranolol (anaprilinum).

D. Decrease of serum calcium.

E. Decrease of potassium concentration in the blood.

6. A patient with chronic cardiovascular insufficiency during digitalization demonstrated the following symptoms: headache,

fatigue, nausea, colour vision impairment (surrounding objects are perceived in green colour). On ECG the sinus bradycardia and signs of impairment of atrioventricular conductivity were detected. What drug can be prescribed to relieve the symptoms of intoxication?

A. Atropine.

B. Naloxone.

C. Bemegride.

D. Dipiroxime.

E. Unithiol.

7. A patient complains of oedemas, rapid pulse, short breath, cyanosis of mucous tunics. The diagnosis is chronic cardiac insufficiency. What drug should be prescribed for this patient?

A. Nitroglycerin.

B. Digoxin.

C. Mesatonum.

D. Cordiaminum.

E. Papaverine.

8. A patient with signs of acute cardiac insufficiency is delivered to a hospital. What drug should be prescribed for urgent aid to this patient?

A. Corglycon.

B. Etimizol (Aethimizolum).

C. Dithylinum.

D. Pyridostigmine bromide.

E. Digitoxin.

9. A patient with cardiac insufficiency took a medicine. Consequently, his heartbeats increased, pulse became stronger, oedema decreased, diuresis increased. What drug did the patient take?

A. Reserpine.

B. Propranolol.

C. Verapamil.

D. Digoxin.

E. Diltiazem.

10. Acute cardiovascular insufficiency is accompanied by edema of lungs. What cardiac glycoside should be prescribed to the patient?

A. Triamterene.

B. Spironolactone.

C. Dichlothiazidum.

D. Acetazolamide (Diacarb).

E. Corglycon.

11. A patient with cardiogenic shock, hypotension, asthma, and oedemas was prescribed a nonglycosidic cardiotonic. Which drug was injected to the patient?

A. Bemegride.

B. Dobutamine.

C. Cordiaminum.

D. Etimizol (Aethimizolum).

E. Caffeine sodium benzoate.

12. A 68-year-old patient with cardiac insufficiency, who had been taking digitalis medicines for a long time, had symptoms of intoxication, which were quickly eliminated by the application of the donator of sulfhydryl groups – unithiol. What is the mechanism of the therapeutic effect of this drug?

A. Increase of energy supply to the myocardium.

B. Reduction of ionized calcium accumulation.

C. Inhibition of potassium release from cardiac histiocytes.

D. Slowing-down of sodium coming into cardiac histiocytes.

E. Reactivation of Na^+, K^+-ATPese of cardiac histiocyte's membranes.

13. Cardiotonic drug was prescribed to a 50-year-old patient with chronic cardiac insufficiency and tachyarrhythmia. What drug was prescribed to patient?

A. Digoxin.

B. Dopamine.

C. Dobutamine.

D. Amiodarone.

E. Mildronate.

14. A patient with complains of frequent pulse, dyspnea, cyanosis of mucous tunics was hospitalized to a cardiological department. Examination revealed oedemas on the lower extremities and ascites. Chronic cardiac insufficiency was diagnosed. What drugs should be prescribed to this patient?

A. Drotaverine hydrochloride.

B. Cordiaminum.

C. Corglycon.

D. Digitoxin.

E. Adrenaline hydrochloride.

15. Extrasystoles, vomiting, disturbances of vision and sleep, alarm, decreasing of diuresis have developed in patient with heart insufficiency in the result of uncontrolled digitoxin using. What group of drugs should be administered to this patient?

A. Donators of NO.

B. Agonists of β_1-adrenergic receptors.

C. Blockers of angiotensin II receptors.

D. Blockers of K^+ channels.

E. Donators of SH-group.

16. A 60-year-old female suffering from ischaemic heart disease for 20 years is delivered to cardiologic department. What drug should be administered to this female for interruption of ciliary arrhythmia attack?

A. Digoxin.

B. Adrenaline.

C. Bicillin V.

D. Laevomycetin (chloramphenicol).

E. Ascorbic acid.

17. Acute heart insufficiency has developed in 60-year-old patient. What drug should be administered to patient?

A. Caffeine sodium benzoate.

B. Adrenaline hydrochloride.

C. Corglycon.

D. Noradrenaline hydrotartrate.

E. Atropine sulfate.

18. A patient suffers from left ventricular insufficiency. Indicate the drug which should be prescribed to him.

A. Piracetam.
B. Digoxin.
C. Etimizol (Aethimizolum).
D. Vinpocetine.
E. Bemegride.

ANTIHYPERTENSIVE DRUGS

Antihypertensive drugs are agents of different chemical structure which able to reduce increased blood pressure.

Hypertensive disease is the most prevalent disease of cardiovascular system. Nearly 25–30 % of word population suffers from hypertensive disease. The frequency of disease is higher in Japan and in highly developed countries of Europe and America. Approximately 80 % of all cases of the increased blood pressure are accounted for essential hypertension. Another 20 % of cases are symptomatic hypertension (renal, endocrinal, etc.).

Different viewpoints exist about primary mechanisms of hypertensive disease. Most common etiotropic factors are psycho-emotional overload and age-related changes in diencephalon-hypothalamus structures of brain. Heredity also plays an important role. In the initial stages of disease, excessive sympathoadrenal system activation is observed. That results in increase of cardiac output, increase of vessels tonus, activation of renin-angiotensin-aldosterone system. Renal changes cause the decrease of sodium and water excretion that results in increase of blood volume. Sodium ions are accumulated in vessels wall that causes the vessels oedema. Simultaneously, ionized calcium level increases in cells of smooth muscles of vessels. Owing to described change, muscular cells sensitivity to vasopressors (catecholamines, angiotensin II, etc.) increases. Hypertrophy of vessels muscular layer develops gradually. These processes are predominantly expressed in small arterioles.

According to their efficacy and meaning in the treatment of hypertensive disease, antihypertensive drugs are classified as follows.

I. Basic antihypertensive drugs:

1) β-adrenoceptor antagonists;

2) inhibitors of angiotensin-converting enzyme and blockers of angiotensin II receptors;

3) diuretics;

4) blockers of calcium channels.

II. Ancillary drugs:

1) α-adrenoceptor antagonists;

2) α, β-adrenoceptor antagonists;

3) central α_2-adrenoceptor agonists;

4) ganglionic blockers;

5) sympatholytic drugs;

6) myotropic antispasmodic drugs;

7) agonists of imidazoline receptors;

8) vasopeptidase inhibitors.

Basic Antihypertensive Drugs

β-Adrenoceptor Antagonists

Owing to likeness of chemical structure of β-adrenoceptor antagonists with catecholamines, these drugs interact with β-adrenoceptors and prevent or eliminate catecholamine influence upon the heart and vessels.

β_1-adrenoceptors are located in myocardium cells, in cardionector, in cells of juxtaglomerular apparatus of kidney, and in fatty tissue. β_2-Adrenergic receptors are located in cells of smooth muscles of bronchi, vessels of skeletal muscles, uterus, liver, pancreas, and membranes of presynaptic ending of sympathetic fibers. In central nervous system, both β_1- and β_2-adrenergic receptors are located.

According to selectivity to types of β-adrenoceptors, drugs are divided into selective β_1-adrenoceptor antagonists and nonselective $\beta_{1,2}$-adrenoceptor antagonists. But if β_1-blockers are used in high

doses, selectivity is worsened. Therefore, correct drug dosage is important.

β-blockers have intrinsic sympathomimetic activity or haven't it. Along with adrenergic blocking activity, β-blockers with intrinsic sympathomimetic activity can stimulate β-adrenoceptors within physiological limits. Due to this, heart rate doesn't significantly decrease at rest. Drugs influence upon activity of sinus node is manifested only during increased physical and emotional stress (that is in case of high catecholamine activity).

On the base of these typical properties, β-adrenoceptor antagonists are classified into several groups:

1) nonselective β-adrenoceptor antagonists or $\beta_{1,2}$-adrenoceptor antagonists:

a) nonselective β-adrenoceptor antagonists without intrinsic sympathomimetic activity: *propranolol (anaprilinum)* and *nadolol (Corgard)*.

b) nonselective β-adrenoceptor antagonists with intrinsic sympathomimetic activity: *pindolol (Visken), oxprenolol (Trasicor),* and *sotalol (Sotalex).*

2) cardioselective β-adrenoceptor antagonists or β_1-adrenoceptor antagonists:

a) drugs without intrinsic sympathomimetic activity: *metoprolol (Vasocardin), atenolol (Tenormin), nebivolol (Nebilet), betaxolol (Lokren),* and *bisoprolol.*

b) drugs with intrinsic sympathomimetic activity: *acebutolol (Secrtal), talinolol (Cordanum), celiprolol (Celiprol).*

Some β-adrenoceptor antagonists have membrane stabilizing activity. This activity is associated with the ability of drugs to decrease membrane permeability for Na^+ and K^+ ions in cardiac conductive system. It promotes antiarrhythmic effect of β-adrenoceptor antagonists. Membrane stabilizing activity is expressed in propranolol, oxprenolol, acebutolol; in less degree – in nadolol, pindolol, metoprolol, and alprenolol.

β-blockers also differ in degree of molecules lipophilicity and ability to penetrate through membranes including blood-brain barrier.

Atenolol is an example of drug with expressive hydrophilic properties which can not penetrate through hematoencephalic barrier. Atenolol lacks sedative effect, has low speed of gastrointestinal absorption and long duration of action. Atenolol is administered once a day. Such drug as propranolol penetrates through blood-brain barrier and exhibits anxiolytic activity.

In recent years, *nebivolol (Nebilet)* is widely used in medicine. Besides β-adrenoblocking activity, the drug stimulates synthesis of nitric oxide that improves coronary circulation and reduces peripheral vascular resistance.

Antihypertensive effect of β-adrenoceptor antagonists is associated with the following mechanisms.

Drugs block β_1-adrenoceptors in the heart, that slows down heart rate, decrease the force of cardiac contraction, cardiac output, and adrenergic reaction to physical exercise. In case of single drug administration, there is 10–25 % decrease of cardiac output level. But in case of regular use, this value is 5–15 %. Drugs with intrinsic sympathomimetic activity decrease the cardiac output in less degree; but it doesn't influence upon their hypotensive activity.

Drugs block β_1-adrenoceptors of juxtaglomerular apparatus cells that results in the decrease of renin secretion, reduces of angiotensin II synthesis and aldosterone release. These changes also promote the reduction of blood pressure.

Lipophilic β-adrenoceptor antagonists penetrate through blood-brain barrier and cause sedation. Prolonged use of these agents results in inhibition of central links of sympathetic nervous system tone regulation.

Nonselective $\beta_{1,2}$-adrenoceptor antagonists block presynaptic β_2-adrenergic receptors, that reduces noradrenaline secretion and decreases excitation of postsynaptic α-adrenoceptors in the vessels and in the heart.

β-adrenoceptor antagonists are administered perorally or parenterally. Lipophilic drugs (*anaprilinum, oxprenolol*, etc.) are readily absorbed in gastrointestinal tract. These drugs bind with

plasma proteins, undergo hepatic biotransformation, and are excreted with bile. These drugs are taken 3 times a day.

Hydrophilic β-blockers (*pindolol, atenolol, nadolol*, etc.) are slowly absorbed in gastrointestinal tract. Degree of their binding with plasma proteins is low. These drugs are excreted in unchanged form through the kidneys. Hydrophilic β-adrenoceptor antagonists are taken 1–2 times a day.

β-adrenoceptor antagonists are prescribed to treat essential and symptomatic hypertension. Initial hypotensive effect develops in several hours after drug intake. Stable decrease of blood pressure is developed gradually; therefore, efficacy of β-blockers should be assessed in 3–4 weeks after initiation of therapy. It is advisable to prescribe β-blockers to patients with hyperkinetic syndrome developing due to physical exercise. Commonly, β-blockers are prescribed in combination with other hypotensive agents. For example, a combination of β-adrenoceptor antagonists with diuretics (e. g., "*Tenoric*") is widely used in medicine to treat hypertensive disease.

Besides, β-adrenoceptor antagonists are used in the treatment for tachyarrhythmias (mainly of supraventricular localization), effort angina resistant to nitrates, hypertrophic cardiomyopathy, and thyrotoxicosis. Drugs also are used to stimulate labor in women with hypertension and to treat parkinsonism of vascular origin.

Therapy with β-adrenoblocker is initiated with its minimal dose which is increased every 2–4 weeks up to optimal therapeutic dose. This dose does not cause hypotension, bradycardia, and water retention in the body.

Clinical use of nonselective β-adrenoblockers is restricted by their most common side effects – bronchospasm and disorders of peripheral blood circulation (intermittent claudication).

Besides, bradycardia and disorders of atrioventricular conduction are observed during therapy with β-adrenoblockers. Heart failure due to use of β-adrenoblockers does not develop as often as expected, because the decrease of blood pressure facilitates the heart

work; and heart work is not worsened even against background of the reduction of cardiac output.

Lipophilic β-adrenoblockers penetrate the central nervous system and can cause insomnia, disturbed sleep, and hallucinations.

Hypoglycemia may be observed in patients with diabetes mellitus who treated by nonselective β-adrenoceptor antagonists, because these drugs inhibit glycolysis. Besides, therapy with β-adrenoblockers is accompanied by worsening of lipid metabolism and increased level of lipoproteins of low- and very low density, that promotes atherosclerosis.

β-adrenoceptor antagonists are not recommended to pregnant women, because drugs increase uterine tone.

Abrupt discontinuation of long-time intake of β-adrenoblockers can lead to "rebound" syndrome. The main manifestations of this phenomenon include hypertensive crisis, angina attacks, and tachyarrhythmias. Phasing out of the drug with the use of another scheme of treatment is most reliable way of prevention of "rebound" syndrome.

Calcium Channel Blockers (Calcium Antagonists)

Calcium channel blockers are classified as follows.

1. First-generation calcium channel blockers: *verapamil (Isoptin), nifedipine (phenigidine),* and *diltiazem.*

2. Second-generation calcium antagonists:

a) verapamil group (phenyl alkyl amine derivatives): *gallopamil, anipamil,* and *falipamil;*

b) nifedipine group (dihydropyridine derivatives): *amlodipine, felodipine, isradipine, nimodipine, nitrendipine, lacidipine,* and *nicardipine;*

c) diltiazem group (benzothiazepine derivatives): *clentiazem*.

3. Third-generation calcium antagonists: *naftopidil, emopamil.*

In comparison with the 1st generation calcium antagonists, 2nd generation drugs are characterized by longer duration of action, higher tissue specificity, and less side effects.

The 3rd generation drugs are characterised by aditional types of activity: naftopidil exhibits α-adrenoblocking activity; emopamil has sympatholytic activity.

Calcium channel blockers block potential-dependent calcium channels in membranes of cardiac histiocytes and smooth muscles of vessels. It results in decrease of total peripheral vascular resistance and decrease of cardiac contraction. Also, calcium channel blockers decrease platelets aggregation, suppress automatism of sinus node and ectopic foci of rhythm in atrium, and slow down conduction through atrioventricular node.

There are the following types of calcium channels: T, N, P, and L. Blockers of calcium channels inhibit the slow L-channels. Intake of these drugs leads to significant reduction of cytoplasmic calcium concentration and relaxation of smooth muscles of arteries. It is proved that intracellular calcium concentration is increased in hypertensive patients, that is considered as the one of the causes of tendency to generalized vasoconstriction. Blockers of calcium channels insignificantly influence venous vessels.

Calcium channel antagonists decrease of myocardial contractile function, that promotes the regression of left ventricle hypertrophy. Unlike other groups of antihypertensive drugs, as a rule therapy by calcium channel antagonists is not accompanied by postural hypotension. Therapeutic doses of calcium channel blockers do not influence normal blood pressure, carbohydrate and lipid metabolism. Therefore, these drugs may be prescribed to patients with diabetes melites. Calcium channel antagonists do not reduce blood circulation in extremities and do not influence physical endurance. The drugs are able to increase the water and sodium excretion from the body.

Calcium channel blockers are administered parenterally, orally, and sublingually. These drugs are readily absorbed in gastroinestinal tract, bind with plasma proteins, penetrate in different tissues and organs including central nervous system. Duration of action of the first-generation drugs is 4–6 hours. Second-generation drugs act up to 12 hours. Calcium channel antagonists undergo high degree of liver biotransformation and excreted mainly by kidneys.

The main indications for use of calcium channel blockers are hypertensive disease, hypertensive crisis, nephrogenic hypertension, hypertension in patients with disorders of cerebral circulation, ischaemic heart disease, and supraventricular tachyarrhythmias, migraine, Raynaud's disease, thrombosis, hypertrophic cardiomyopathy, and cold-induced bronchoconstriction.

Such drugs as nifedipine, felodipine, and diltiazem are effective at monotherapy of hypertensive disease of mild and moderate severity. Stable effect developed in 1–2 weeks after initiation of therapy. Tachycardia may be observed at the initiation of the treatment, aspecially in the young patients. At severe hypertensive disease, calcium channel antagonists are combined with β-adrenoblockers and angiotensin-converting enzyme inhibitors.

At the last time, there is tendency when short-acting calcium antagonists are replaced by drugs with long-lasting effect (e. g., nitrendipine, felodipine, amlodipine). Nitrendipine's activity is three times higher than activity of nifedipine. The drug causes systemic vasodilation with the decrease of peripheral vascular resistance. Besides, nitrendipine dilates renal vessels, increases excretion of sodium ions and water, and increases the blood level of natriuretic hormone. Most pronounced effect is observed in elderly patients with hypertension against the background of the low renin level. Long-time use of nitrendipine causes the regression of myocardial hypertrophy. The drug is taken once a day. At hypertensive crisis, nitrendipine may be used sublingually.

Felodipine exhibits marked influence upon the vessels. The drug does not cause negative inotropic effect and does not influence conductibility of the heart. Felodipine is effective at hypertensive disease of any degree of severity, including elderly patients with renovascular hypertension. In comparison with nifedipine, the drug exhibits higher efficacy in case of its combination with diuretics and β-adrenergic antagonists.

Side effects of calcium antagonists include headache, dizziness, flushing, constipation, oedema of feet, shins, and elbows owing to vascular stasis, and disturbances of microcirculation. Also, both bradycardia (for verapamil) and tachycardia (for nifedipine) are possible.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are divided into three generations:

– I-generation drugs: *captopril (Capoten), methiapril*;

– II-generation drugs: *enalapril, lisinopril, ramipril, benazepril, fosinopril, perindopril, trandolapril*;

– III-generation drugs: *zofenopril*.

The I-generation drugs contain HS-group in their molecular structure.

The II-generation drugs contain carboxyl or phenolic groups in their molecules. These drugs are characterized by higher activity, lack of sulfhydryl groups in molecules, longer duration of action, less frequency of side effects.

Renin is synthesized in juxtaglomerular cells in the result of sympathetic stimuli, reduction of renal blood flow, decrease of blood pressure, and increase of sodium concentration in distal convoluted tubules. Renin influence angiotensinogen and cleaves from it angiotensin I. Angiotensin-converting enzyme (kinase II) transforms angiotensin I to angiotensin II. Synthesis of angiotensin II occurs in the heart, brain, lungs, and other organs. High concentration of ACE is found in vascular endothelium. In the adrenal glands, angiotensin II is metabolized into angiotensin III. Angiotensins II and III stimulate the aldosterone release, that increases of the renal reabsorption of sodium and water and stimulates the potassium excretion. Also, angiotensins II and III increase vascular rigidity and stimulate collagen synthesis, that promotes myocardial fibrosis.

There are 4 types of angiotensin II receptors. The main cardiovascular effects are due to excitation of angiotensin receptors of the first type (AT_1). Angiotensin II causes significant vasoconstriction and stimulates cardiac contractions. Besides, angiotensin II acts as growth factor of cardiac histiocytes and vascular smooth muscle cells, increases secretion of vasopressin, prolactin, and adrenocorticotropin.

It should be noticed that ACE also catalyzes inactivation of bradykinin and enkephalins. Bradykinin and enkephalins relax

vessels, decrease blood pressure, increase sodium and water excretion, retards potassium in the body, and suppress platelets aggregation.

ACE inhibitors decrease angiotensin II synthesis and, therefore, prevent its effects. Besides, these drugs promote bradykinin and enkephalin protection that results in the increase of their effects. Owing to this mechanism, ACE inhibitors cause the following effects:

– both venous and arterial tone is decreased;

– blood pressure is lowered;

– both preload and afterload upon the heart is diminished;

– blood circulation in heart, kidneys, and other inner organs is improved;

– secretion and activity of atrial natriuretic peptide is increased;

– diuresis is increased.

Also, ACE inhibitors suppress lipid peroxidation and improve carbohydrate metabolism.

It should be noted that the application of ACE inhibitors is accompanied by decrease of hypertrophy of myocardium and vascular wall. ACE inhibitors decrease the possibility of ventricular arrhythmias.

ACE inhibitors are prescribed orally. Enalapril (Vasotec) and lisinopril are also administered intravenously. Taken orally drugs are readily absorbed from gastrointestinal tract. Absorption of ACE inhibitors is independent from food, except captopril which should be taken in 2–3 hours before a meal. Most drugs bind with plasma proteins in high degree. Only captopril and lisinopril are characterized by low degree of binding with proteins which is 20–30 %. ACE inhibitors easily penetrate in different tissues of the body.

Therapeutic effect of captopril develops in 1 hour after intake. Onset of effect of other drugs is 2 hours after oral intake. Duration of captopril action is 6 hours; other drugs act up to 24 hours. In this regard, captopril is taken 4 times a day; other drugs are prescribed once a day. The main route of drugs elimination is kidneys. But such

drugs as ramipril, benazepril, and perindopril are predominantly excreted by liver (approximately 60 % of the administered dose).

Trandolapril is one the most effective and long-acting ACE inhibitors. Its ability to inhibit ACE is in 6–10 times more than those of enalapril. Trandolapril acts up to 48 hours.

ACE inhibitors increase blood circulation in myocardium, liver, brain, and kidneys. The drugs efficacy is proportional to blood renin concentration. And while drugs reduce blood pressure in patients with normal renin activity, drugs efficacy in this case is less.

ACE inhibitors are effective at mild, moderately severe, and refractory to other drugs hypertensive disease. These drugs are combined with centrally acting hypotensive agents, calcium channel blockers, β-adrenoceptor antagonists, and diuretics. To prevent marked hypotension, ACE inhibitors initially should be taken in low doses. Captopril may be used sublingually to cessate hypertensive crisis.

Nowadays, ACE inhibitors are used in the treatment for chronic heart failure. Owing to reduction of arterial and venous tone, these drugs decrease preload and afterload upon the heart, and blood pressure in ventricles. In three months after the initiation of treatment with ACE inhibitors, hypertrophy of the left ventricle is significantly reduced.

ACE inhibitors are also used in postinfarction cardiosclerosis and diabetic nephropathy. At the last patology, these drugs dilate an efferent artery and decrease intraglomerular hypertension which is the main cause of glomerulosclerosis.

Intake of ACE inhibitors can lead to excessive hypotension. This complication is more likely in patients which were treated by high doses of diuretics prior therapy by ACE inhibitors.

Therapy by ACE inhibitors is often accompanied by dry cough which is refractory to action of antitussive drugs. This cough is due to inhibition of bradykinin inactivation and increase of prostaglandin E_2 synthesis in the bronchi. These phenomena can also lead to development of anhioedema.

ACE inhibitors can cause skin allergic reactions, neutropenia, metallic taste in mouth, headache, dizziness, and hyperkalemia.

Dispite of significant number of side effects, therapy by ACE inhibitors has no age limit. Discontinuation of ACE inhibitors intake does not lead to rebound effect. But long-time therapy by ACE inhibitors is accompanied by slow developing tolerance.

It should be noticed that some patients are resistant to ACE inhibitors, because angiotensin II synthesis is regulated, except ACE, by other enzymes (chymases, cathepsins, etc.). In this case, blockers of angiotensin receptors more completely inhibit renin-angiotensin system.

Blockers of Angiotensin Receptors

Angiotensin receptor blockers include such drugs as *losartan (Cozaar), valsartan (Diovan), candesartan, irbesartan, telmisartan,* etc.

The first approved for clinical use drug of this group saralasin is not used nowadays. Losartan was approved in 1992; later, other angiotensin receptor blockers was created.

Drugs block AT_1 angiotensin receptors in vessels, adrenal gland and other organs, decrease concentrations of aldosterone and norepinephrine in the blood. Besides, angiotensin receptor blockers increase renal excretion of sodium and exhibit diuretic action.

Consequently, total peripheral vascular resistance, systemic blood pressure, and pressure in the pulmonary circulation are reduced. Blockage of AT_1 receptors leads to the increase of blood level of renin, angiotensin I, and angiotensin II. The increase of angiotensin II concentration results in stimulation of AT_2 receptors that is accompanied by activation of natriuresis and relaxation of vessels due to NO release. Also, activation of AT_2 receptors leads to inhibition of endothelial proliferation. It should be noticed that natriuretic and diuretic effects also promote the vasodilation. Angiotensin receptor blockers do not influence bradykinin metabolism. Hypotensive activity of angiotensin receptor blockers is

identical to the activity of ACE inhibitors, but these drugs are tolerated by patients better.

Angiotensin receptors blockers are taken orally once a day. Their bioavailability is approximately 30 %. Antihypertensive effect develops for 6 hours and lasts up to 24 hours. Unchanged drugs and their metabolites are excreted by liver. Maximum effect is obcerved in 3–6 weeks of permanent therapy and kept long time after phasing out of the drug.

Angiotensin receptor blockers are used to treat hypertensive disease, renovascular hypertension, for diagnostics of increased activity of renin-angiotensin system, and chronic cardiovascular insufficiency.

Side effects of angiotensin receptor blockers include headache, vertigo, postural hypotension, hypokalemia, cough, and allergic reactions. Besides, angiotensin receptor blockers exhibit teratogenic action, therefore these drugs are contraindicated in pregnancy.

Diuretics

Hydrochlorothiazide (dichlothiazidum), chlortalidone (Oxodolinum, Hygroton), furosemide, clopamide (Brinaldix), indapamide, spironolactone, triamterene and other diuretics are used to treat hypertensive disease.

Diuretics reduce sodium and water reabsorption and decrease the volume of extracellular fluid. These drugs exhibit own hypotensive effect and significantly potentiate effect of other antihypertensive drugs. Drugs are widely used for monotherapy of initial stage of hypertensive disease. Different diuretics are often used together for potentiation of their action and for diminish of side effects. Thiazides (hydrochlorothiazide), non-thiazide sulfonamides (chlortalidone, clopamide, indapamide), and potassium-sparring diuretics (triamterene, amiloride, spironolactone) are most widely used diuretics for treatment of hypertensive disease. Strongly acting loop diuretics (furosemide, etacrynic acid, torasemide) are used to treat aggravation of II and III stages of hypertensive disease and to arrest

hypertensive crisis. It should be noticed that diuretics with low and moderate efficacy do not influence blood pressure in healthy people.

Initially, diuretics decrease blood pressure due to the increase of sodium and water excretion and reduction of circulating volume. In 6–8 weeks after therapy initiation, diuretic effect is gradually decreased, and cardiac output is normalized. It is due to the increase of renin activity in result of the reduction of plasma volume and blood pressure. Under the circumstances, hypotensive effect of diuretics is associated with the decrease of peripheral vascular resistance. Likely, reduction of vascular tone is the result of gradual decrease of intracellular sodium and increase of intracellular potassium in cells of vascular wall. Despite of increased activity of renin-angiotensin system, resistance of peripheral and renal vessels is reduced. Diuretics decrease both systolic and diastolic blood pressure and maintain or even increase cardiac output. Diuretic drug therapy is not accompanied by postural hypotension.

Hydrochlorothiazide (hypothiazid, dichlothiazidum) is most widely used diuretic in the treatment for hypertensive disease. Usually, the drug is taken two times a day in individual doses.

Recently, the new group of diuretics with vasodilating effect was approved in medicine. Indapamide and its prolonged form *Indapamide retard* are representatives of this group. At treatment of hypertension, long-acting drugs (Indapamide retard, chlortalidone, and clopamide) are preferable. These drugs are taken once a day or once in 1–2 days.

Excessive diuretic effect leads to muscular weakness (due to potassium loss), dry mouth, paresthesia, and thirst. For prevention of hypokalemia, potassium-contaning drugs are prescribed (e. g., potassium chloride, Asparcam, Panangin); or thiazide diuretics are combined with potassium-sparing agents. Besides, diuretics (e. g., thiazides) decrease calcium level in the blood, cause hyperglycemia, hyperuricemia, and increase cholesterol concentration in the blood.

Supporting Antihypertensive Drugs

Vasopeptidase Inhibitors

Recently, new group of hypotensive drugs – vasopeptidase inhibitors – was approved in medicine. The representatives of this group are *omapatrilat* and *aladotrilat*.

Vasopeptidases are presented by two enzymes of cellular membrane – angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP, neprilysin). The last enzyme catalyzes inactivation of vasodilator peptides (natriuretic peptide, bradykinin, and adrenomedullin).

Omapatrilat inhibits the activity of ACE and neprilysin that leads to the decrease of angiotensin II concentration and the increase of concentration of vasodilator peptides. Due to such mechanism, omapatrilad decreases peripheral vascular resistance, circulating blood volume, blood pressure, and afterload. Besides, omapatrilat exhibits cardioprotective action.

Omapatrilat is taken orally one time a day. The drug is readily absorbed in gastrointestinal tract. Its bioavailability is about 30 %. Omapatrilat binds with plasma proteins, undergoes nepatic metabolism, and is excreted mainly by kidneys. Duration of omapatrilat's action is about 24 hours.

Omapatrilat is used to treat hypertensive disease and chronic heart failure.

Side effects of omapatrilat are headache, cough, dyspeptic disorders, and skin rash.

α-Adrenoceptor Antagonists

α-Adrenoceptor antagonists are divided into:

– α_1-adrenoceptor antagonists: *prazosin, doxazosin, terazosin*;

– $\alpha_{1,2}$-adrenoceptor antagonists: *phentolamine, tropaphenum, pyrroxane*.

Nonselective α-adrenoceptor antagonists relax vessels owing to blockage of both α_1 and α_2-adrenoceptors. But these drugs aren't

used for systemic treatment of hypertensive disease because they don't promote stable hypotensive effect. Shortness of effect is the result of blockage of presynaptic α_2-adrenoceptors which regulate negative feedback. Blockage of these receptors results in excessive noradrenaline release and restoration of adrenergic transmission in vessels. Nonselective α-adrenoceptor antagonists are used in the treatment for pheochromocytoma (tumor of adrenal gland medulla), hypertensive crisis, and pulmonary oedema.

Stable and prolonged blockage of postsynaptic α-adrenergic receptors is observed in prescribing of selective α_1-adrenoceptor antagonists (prazosin, doxazosin, etc.) because these agents don't affect negative feedback in adrenergic synapses. Blockage of α_1-adrenoceptors in vessels leads to the decrease of general peripheral resistance, venous return, and left ventricular preload. Hypotensive effect of α_1-adrenoceptor antagonists isn't accompanied by tachycardia and elevation of cardiac output. Prazosin and doxazosin additionally exhibit moderate antispasmodic influence upon vascular smooth muscles. Also, both drugs decrease concentration of low-density lipoproteins and of very low-density lipoproteins. This effect is very useful in case when arterial hypertension is accompanied by hyperlipidemia.

At oral intake, selective α_1-adrenoceptor antagonists are readily absorbed in gastrointestinal tract. These drugs are xcreted from the body mainly with feces; only insignificant amount of administered dose is excreted by kidneys. Prazosin is prescribed two times per day, doxazosin – once a day.

Indications for use of selective α_1-adrenoceptor antagonists are the following: hypertensive disease, chronic heart failure, chronic renal failure, and pulmonary hypertension. It should be noticed that the absence of influence upon carbohydrate metabolism allows to use these drugs in patients with accompanied diabetes mellitus. Prazosin and doxazosin are also used to treat benign prostatic hyperplasia and hypertension of pregnancy.

Side effects of selective α_1-adrenoceptor antagonists include headache, excessive hypotension, drowsiness, diarrhoea, nasal congestion, dry mouth, polyarthritis, frequent urination, and female urinary incontinence.

α-, β-Adrenoceptor Antagonists

Labetalol (*Trandate*) and *carvedilol* (*Dilatrend*) are drugs blocking both α- and β-adrenergic receptors.

Labetalol blocks β_1, β_2, and α_1-adrenergic receptors. Wherein, its β-adrenoblocking activity is 3 times more than ability to block α-adrenoceptors. The drug is taken orally to treat arterial hypertension of administered intravenously to treat hypertensive crisis. Labetalol is readily absorbed in gastrointestinal tract, metabolized by liver, and excreted by kidneys in form of metabolites. The drug dilates vessels and decrases blood pressure without significant influence upon cardiac output. Its duration of action is 8–10 hours. At regular long-time intake, labetalol decreases heart rate and prevents the increase of force of cardiac contraction at physical activity. Side effects of labetalol are dizziness and postural hypotension.

Carvedilol (Dilatrend) is 10–100 times more potent blocker of β-adrenoceptors than labetalol. Also, its α-adrenoblockering activity is 1.5–3 times more. Simultaneously, carvedilol exhibits antioxidative activity. The drug decreases peripheral vascular resistance, renin blood concentration, cardiac preload and afterload. Carvedilol is taken orally. Its hypotensive effect lasts up to 15 hours. The drug is used to treat hypertensive disease, ischaemic heart disease, and chronic heart failure. Its possible side effects are headache, bronchoconstriction, skin rash, and fatigability.

Central α_2-Adrenoceptor Agonists

Clonidine (*clopheline, Catapresan*) and *methyldopa* (*Dopegyt, Aldomet*) excite α_2-adrenoceptors in neuronal membranes of vasomotor centre that is accompanied by inhibitory effect. Antihypertensive effect is due to the inhibition of pressor part of vasomotor centre and general decrease of sympathetic innervation tone. It is accompanied by the decrease of peripheral vascular resistance and heart rate, reduction of catecholamines secretion by adrenal glands, and temporally decrease of renin production.

Clonidine (clopheline) is one of the most potent and fast-acting hypotensive agents. The drug is an agonist of α_2-adrenergic and I_1-imidazoline receptors. Stable hypotension may be preceded by the short-time (before penetration of the drug in central nervous system) increase of blood pressure due to excitation of vascular α_2-adrenergic receptors. This phase lasts 5–10 minutes. Hypotensive effect of clopheline lasts 10–12 hours. As a rule, clonidine therapy is started with small doses which are taken 2–4 times a day. Clonidine dose is gradually increased.

So-called rebound syndrome develops due to disinhibition of sympathetic centres at sudden phasing out of clopheline intake. It starts in 18–36 hours after cessation of the drug intake and lasts from 1 to 5 days. Rebound syndrome symptoms are the increase of blood pressure up to hypertensive crisis, tachycardia, encephalopathy, heart rhythm disorders, and abdominal pain. Small doses of clopheline in combination with β-adrenergic antagonists are used to arrest rebound syndrome. Slow decrease of clonidine dose allows to avoid return syndrome. Gradual phasing out of clopheline intake lasts at least 7 days.

Clopheline is taken orally and administered parenterally. The drug is readily absorbed in gastrointestinal tract and excreted from the body by kidneys. Clopheline is used to treat hypertensive disease and to arrest hypertensive crisis.

Clonidine easily penetrates central nervous system and exhibits hypnotic and sedative effects, decreases the body temperature. The drug potentiates effects of ethyl alcohol and other central nervous system depressants. Clopheline increases appetite, decreases secretion of salivary glands. Clopheline therapy is accompanied by such side effects as postural hypotension, dry mouth, constipation, urinary retention, visual disordes, sodium and water retention, etc. Long-time clopheline intake leads to tolerance that needs to increase drug dose in 2–5 times. Clonidine reduces renal circulation due to renin hyperproduction. Slowdown of blood circulation in brain, retina, and lower extremities promotes thrombosis.

Methyldopa is transformed to α-methyl-norepinephrine which stimulates postsynaptic α_2-adrenoceptors in neuronal membranes of vasomotor centre. It leads to the vasodilation and reduction of total peripheral vascular resistance. Also, decreased cardiac output is observed at initialization of therapy. Drug relaxes renal vessels and increases diuresis. Besides, methyldopa exhibits sedative and hypnotic effects. The drug is taken orally or administered parenterally once a day.

Therapy by methyldopa is accompanied by such side effects as weakness, fatigue, disorder of attention, drowsiness, dry mouth, nasal stuffiness, dizziness, dyspepsia, and skin rash. Sometimes, methyldopa intake is aggravated by agranulocytosis, hemolytic anemia, and thrombocytopenia. In comparison with clopheline, postural hypotension is less common. The described side effects be found more often in aged patients. Long-time intake of methyldopa leads to tolerance. Small doses of methyldopa may be prescribed with diuretics and β-adrenergic antagonists. It should be noticed that combination of methyldopa with central nervous system depressants increases hypotensive action, but combination with MAO inhibitors provokes hypertensive crisis.

Ganglionic Blockers

Ganglionic blockers include such drugs as *benzohexonium (hexamethonium), pentamine (azamethonium bromide), pirilenum (pempidine), hygronium (trepirium iodide),* and *arfonad*. Drugs block N_n-cholinergic receptors in sympathetic ganglia and prevent propagation of sympathetic vasoconstrictive impulses to vessels. Administration of ganglionic blockers is accompanied by significant dilation of arterioles, venules, and capillaries that leads to the decrease of blood pressure. Due to inhibition of reflexes which maintain stable level of blood pressure at change of body posture, ganglionic blockers can provoke postural hypotension. Cardiac output and stroke volume are decreased mainly owing to reduction of venous return to the heart. Dilation of veins is accompanied by reduction of cardiac preload. Blood is deposited in

vessels of mesentery and lower extremities. The reduction of blood pressure is observed in pulmonary circulation and in right ventricle. Circulating blood volume is decreased. Peripheral vascular resistance and left ventricle afterload are reduced due to dilation of small arteries, arterioles, and metarterioles.

Ganglionic blockers with short action (hygronium, arfonad) are used for controlled hypotension during surgical operation. Besides, ganglionic blockers are used in the treatment for pulmonary and brain oedema and to arrest hypertensive crisis. Nowadays, ganglionic blockers are scarcely used to treat hypertensive disease, because their administration results in significant number of side effects: decrease of tone and motility of gastrointestinal tract and bladder, constipation, accomodation disorder, and dry mouth. The most serious complication of ganglionic blocker administration is postural hypotension. Regular intake of ganglionic blockers leads to tolerance.

Sympatholytics

Sympatholytics *reserpine* and *octadine* inhibit adrenergic transmission due to influence upon presynaptic membranes of adrenergic nerves. These drugs exhaust noradrenaline storage.

Reserpine is alkaloid of *Rauwolfia.* The drug violates the deposition of noradrenaline in vesicles and promotes its inactivation by MAO. Hypotensive action of reserpine is mainly due to its peripheral effects: vasodilation, decrease of total peripheral resistance, bradycardia, and decrease of cardiac output. But reserpine also reduces noradrenaline storage in central nervous system that leads to the decrease of vasomotor centre tone and reduces the activity of limbic system and reticular formation. Therefore, reserpine exhibits psychosedative and hypnotic effects and provokes depression. Reserpine is taken orally once a day. Its hypotensive effect develops in 1–5 days after therapy initiation. After phasing out of the drug intake, hypotensive effect persists during 3–4 weeks. Rebound syndrome is not characteristic of reserpine intake discontinuation. Reserpine does not cause postural hypotension.

Reserpine is weak hypotensive agent and, as a rule, is a component of the co-formulated drugs *("Normatens"*, etc.).

Side effects of reserpine are determined by its mechanism of action. Thus, long-time intake of reserpine in usual hypotensive doses (1 mg a day), especially by aged patients, may be accompanied by depression and parkinsonism due to exhaustion of dopamine storage in the brainstem nuclei. Increased parasympathetic influence upon inner organs is accompanied by elevation of secretion and motility of gastrointestinal tract (hypersalivation, exacerbation of ulcer disease and gastritis, and diarrhea), increase of bronchial tone, bradycardia, nasal congestion, etc. Reserpine potentiates hypotensive action of diuretics, ganglionic blockers, and peripheral vasodilators. Combination of reserpine with antiarrhythmic drugs and cardiac glycosides should be used carefully.

Octadine violates noradrenaline release and prevents its neuronal reuptake. The drug is poorly soluble in lipids and does not penetrate central nervous system. At initiation of the treatment, octadine decreases cardiac output. Long-time intake of octadine is accompanied by reduction of total peripheral resistance and venous blood return to the heart. Drug is taken orally once a day. Hypotensive effect develops in 4–7 days after initiation of treatment. After phasing out of the drug, its hypotensive effect persists 1–2 weeks. Octadine can cause postural hypotension. Other side effects include bradycardia, atrioventricular conduction disorders, increased bronchial tone, diarrhoea, nasal stuffiness, etc.

Potassium Channel Activators

Potassium channel activators are *diazoxide* and *minoxidil*. These drugs activate (open) potassium channels in membranes and promote K^+ output from the cells that is accompanied by membrane hyperpolarization and inactivation of calcium channels. Under these circumstances, the sensitivity of smooth muscles to vasoconstrictive agents (catecholamines, angiotensin II, etc.) is sharply decreased. Potassium channel activators dilate only arterioles. Their hypotensive effect is due to reduction of total peripheral vascular resistance.

Minoxidil is one of the most potent drugs of this group. Drug is used to treat most severe and malignant forms of hypertension, which are resistant to other hypotensive agents and their combinations. Minoxidil significantly decreases blood pressure and reduce cardiac afterload. The drug is taken orally. Minoxidil is readily absorbed in gastrointestinal tract and excreted from the body mainly by kidneys. Its hypotensive effect lasts 24 hours. Side effects of minoxidil are hirsutism, pericardium lesion, skin rash, thrombocytopenia, leukopenia, headache, sodium and water retention in the body.

Diazoxide is more potent hypotensive agent than minoxidil. The drug is administered intravenously to arrest hypertensive crises. Effect develops in 2–5 minutes and lasts 6–18 hours. Besides reduction of arterioles tone, diazoxide suppresses the heart activity. Drug inhibits secretion of insulin and causes hyperglycemia. Side effects include sodium and water retention and increased blood concentration of uric acid. The drug is potent relaxant of uterus. Oral diazoxide (*Proglycem*) is used to treat hypoglycemia associated with hyperinsulinism (e. g., in patients with inoperable islet cell carcinoma).

Nitric Oxide Donators

Sodium nitroprusside is hypotensive agent influencing resistance and capacitance vessels. Hypotensive effect of drug is not accompanied by the increase of cardiac output. Mechanism of action of nitroprusside is similar to nitroglycerin's mechanism. In the body, sodium nitroprusside releases nitrous oxide which stimulates cytosolic guanylate cyclase. Due to this, the level of cGMP is increased, and intracellular calcium concentration is reduced. Hereby, tone of smooth muscles of vessels is decreased.

Sodium nitroprusside is administered intravenously drop-by-drop to arrest hypertensive crises, for controlled hypotension, and to treat pulmonary oedema and acute left ventricular failure. Hypotensive effect develops in 2–3 minutes. Drug administration is accompanied by tachycardia, headache, dyspeptic disorders, and muscular twitching.

Miscellaneous Drugs

Apressinum (*hydralazine*) moderately relaxes resistance vessels, decreases total peripheral resistance and blood pressure. Drug is taken orally. Apressinum is readily absorbed in gastrointestinal tract, bind with plasma proteins. For dosage of drug, it is necessary to remember that speed of its metabolism is dissimilar in different patients. As a rule, the drug effect lasts 6–8 hours. Side effects of hydralazine include tachycardia, heart pain, arrhythmias, myocardial infarction, headache, water-salt balance disorder, autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, etc.), dyspepsia, etc. Hydralazine is contraindicated at stenocardia, myocardial infarction, ulcer disease of stomach, and systemic lupus erythematosus.

Dibazolum (*bendazol*) exhibits antispasmodic action upon all inner organs containing smooth muscles. The drug decreases blood pressure due to vascular relaxation, reduction of total peripheral resistance and cardiac output. Hypotensive effect of dibazolum is moderate and short-lasting. As a rule, dibazolum is combined with other hypotensive agents to treat hypertensive disease. Also, the drug is administered intramuscularly or intravenously to arrest hypertensive crisis, aspecially with phenomena of encephalopathy. Side effects appear seldom.

Magnesium sulfate is administered intravenously or intramuscularly to arrest hypertensive crises. Besides myotropic spasmolytic action, drug also suppresses neurotransmission in vegetative ganglia. High doses of magnesium sulfate inhibit vasomotor centre. Also, the drug exhibits sedative effect and inhibits convulsions. Magnesium sulfate is characterized by narrow margins of safety. The drug overdose leads to respiratory depression. Calcium ions are antagonists of magnesium ions; therefore, calcium chloride is administered at overdose of magnesium sulfate.

Papaverine is alkaloid of opium which is obtained by means of synthetic way. It is myotropic antispasmodic agent. The drug inhibits phosphodiesterase activity that leads to accumulation of intracellular cAMP with the following relaxation of smooth muscles.

The drug exhibits vasodilating and spasmolytic effects. High doses of papaverine suppress the excitability of myocardium and slows down intracardiac conduction. Papaverine has weak sedative action upon central nervous system. The drug is used in the treatment for vascular spasms (including cerebral vessels) and spasms of smooth muscles of bronchi and organs of abdominal cavity. Side effects appear seldom.

No-Spa (*drotaverine*) has properties similar to papaverine but exhibits more expressed and longer spasmolytic action. The drug is used alone or in combination with nicotinic acid (*Nicospan*).

Pentoxifylline (*Trental*) improves microcirculation and rheological properties of blood. The drug dilates vessels and increases oxygen delivery to the tissues. Its mechanism of action is associated with blockage of adenosine receptors and inhibition of phosphodiesterase that leads to cAMP accumulation in vascular smooth muscles and thrombocytes. Besides, pentoxifylline decreases platelet aggregation, increases erythrocyte elasticity, and decreases blood viscosity. The drug is taken orally and administered intravenously or intramuscularly.

Imidazoline Receptor Agonists

Moxonidine (*Physiotens*) and *rilmenidine* stimulate I_1-imidazoline receptors of vasomotor centre in medulla oblongata that results in reduction of sympathetic nervous system activity. Moxonidine exhibits high hypotensive activity. The drug is taken once a day. In comparison with clopheline amount of side effect of moxonidine is significantly less. Hypotensive activity of rilmenidine is superior of moxonidine. Both drugs do not cause rebound syndrome.

Principles of Hypotensive Drugs Combination

Treatment of hypertensive disease is a difficult problem requiring perseverance and attention of both doctor and patient. There is initial transitory stage in development of hypertensive disease, when blood pressure increases episodically due to influence of stress. Gradually, periods with normal blood pressure become shorten, but periods with insignificantly increased blood pressure are drown out. At this stage, patients visit a doctor seldom, whereas arterial hypertension is successfully treated namely at this stage. At this period, patients should restrict consuming of sodium chloride, fluids, to avoid stress, to refuse from bad habits, and streamline work and rest. Medicinal herbs fees with hypotensive and sedative properties and small doses of tranquilizers are used to treat this stage of hypertensive disease. But, intake of hypotensive drug is also possible. These patients need medical supervision during several years even in case of full normalization of blood pressure.

But patients visit a doctor only at stage when patology became stable. In case of I ("mild") stage of hypertension when diastolic blood pressure is within 95–104 mm Hg, intake of drugs is obligate, and treatment lasts long time. At II ("moderate") stage of hypertension when diastolic blood pressure is 105–115 mm Hg, lifelong pharmacotherapy is necessary. The aim of treatment is to stop disease progress and to prevent hypertensive crises.

At III ("severe") stage of hypertensive disease when diastolic blood pressure is 115 mm Hg and higher, pharmacotherapy is difficult and is carried out with aim to delay maximally the development of severe complications (insult, infarction, heart and renal failure).

Antihypertensive drugs are prescribed according to so-called step scheme of hypertensive disease treatment. There are four steps of hypertensive disease therapy. Monotherapy is used during first step of treatment (at I–II stages of hypertensive disease). It should be noticed that there is no universal drug to treat all patients. Treatment is initiated by minimal effective doses of chosen drug. Its dose is gradually increased but the dose, when side effects appear, no

achieved. Wherein, blood pressure is decreased gradually, and long-time periods of high blood pressure are not observed. If effect is absence in 2–4 weeks after therapy initiation, it is necessary to replace the drug by another. The hypotensive drugs of basic group are used for monotherapy.

When monotherapy is ineffective, two drugs are prescribed to treat hypertensive disease. The effect of potentiation allows to prescribe both drugs in minimal doses. Chosen drugs should to defuse the side effects one of another. As a rule, the drugs of basic group are combined, but supporting hypotensive drugs are also used.

At the third level of hypertensive disease treatment, the third agent of basic or supporting group is added to scheme of therapy. It is forced step because the less quantity of taken drugs, the more easily is control of the result.

At progress of hypertension, patient needs the fourth stage of treatment when strongly acting drugs (octadine, minoxidil, etc.) or some drug of basic group, which are not used previously, are included in scheme of the treatment. The task of this stage is not only to control blood pressure, but also to restore regional circulation and cardiac and renal functions. Prevention of hypertensive crises is the most important task of this stage because crises become more dangerous due to further progress of hypertensive disease.

Commonly, co-formulated drugs are used to treat hypertension: *"Tenoric"* (contains atenolol and hydrochlorothiazide), *"Capozide"* (captopril and hydrochlorothiazide), *"Enap-H"* (enalapril and hydrochlorothiazide), *"Logimax"* (metoprolol and felodipine), *"Hyzaar"* (losartan and hydrochlorothiazide), etc. These co-formulated drugs provide long-time and stable hypotensive effect.

Drugs Used to Arrest Hypertensive Crisis

Hypertensive crisis is a sharp eleveation of blood pressure which accompanied by headache, “gray tog”, “seeing spots”, irritability, tachycardia, chest pain, nausea, vomiting, etc. Hypertensive crisis can cause insult, acute left ventricular failure with pulmonary oedema, myocardial infarction, fast progression of renal failure. The treatment of hypertensive crisis is an emergency care task.

According to classification of Ukrainian association of cardiologists (1999), hypertensive crises are divided into two types:

– complicated crisis – states with progressive damage of different organs (insult, myocardial infarction, bleeding, acute renal failure, etc.) which are dangerous for patient life and need immediate (within 1 hour) reduction of blood pressure;

– noncomplicated crisis – states without acute or progressive damage of different organs which are potensially dangerous for patient life and need to reduce blood pressure during several hours (up to 24 hours).

The patient should be in a sitting or half-sitting position. The treatment of hypertensive crisis begins with intravenous administration of hypotensive drugs with fast onset of action. For long-time hypotensive effect, the drugs are also administered intramuscularly. Blood pressure is monitored.

Sodium nitroprusside, nitroglycerin, diazoxide, labetalol, esmolol, propranolol, furosemide, torasemide, magnesium sulfate, verapamil, clopheline, phentolamine, enalaprilat, nimodipine, and other drugs are administered to arrest hypertensive crisis. For first hours, blood pressure should be decreased 20–25 %. Fast reduction of blood pressure can provoke dangerous complications (coma, angina pectoris attack, arrhythmias, etc.).

Therapy of noncomplicated crises does not require intravenous drug administration. *Clopheline, nifedipine, captopril, prazosin, propranolol,* and *labetalol* are taken orally of sublingually. Also, such drugs as *bendazole, pyrroxane, diazepam, furosemide, torasemide,* and *clopheline* may be administered intramuscularly.

Aminazine (intramuscularly, 50–100 mg) or *droperidol* (intramuscularly or intravenously, 5 mg) are administered to patients with high tone of sympathoadrenal system, vomiting, anxiety, and other symptoms of encephalopathy.

HYPERTENSIVE DRUGS

Drugs which increase blood pressure are used to treat shock of different genesis, collapse, arterial hypotension, and allergic reactions which accompanied by reduction of blood pressure. The cause of hypotension should be identified before drug administration. Pathogenetic therapy in any cases includes administration of drugs increasing blood pressure.

Hypertensive drugs are classified according mechanism of action as follows.

1. Drugs stimulating vasomotor centre – analeptics: *caffeine, cordiaminum, camphor, sulfocamphocaine*.

2. Drugs which tone central nervous system and cardiovascular system: *pantocrinum, tinctures of Ginseng, Schizandra; extracts of Eleutherococcus, Rhodiola*.

3. Drugs with peripheral vasoconstrictor and cardiotonic activity.

3.1. Drugs which stimulate both α- and β-adrenergic receptors in vessels and heart: *norepinephrine, epinephrine, ephedrine*.

3.2. Drugs which stimulate α-adrenergic receptors: *mesatonum (phenylephrine)*.

3.3. Gormonal drugs: *vasopressin, pituitrin*.

3.4. Agonists of dopaminergic receptors: *dopamine*.

3.5. Drugs with peripheral action: *angiotensinamide*.

3.6. Drugs selectively stimulating β_1-adrenergic receptors: *dobutamine*.

4. Drugs increasing blood volume: *polyglucinum, rheopolyglucin, Neohaemodes.*

Dopamine exhibits dose-dependent effects. Small doses of dopamine (1–5 mg/kg in 1 minute) stimulate peripheral dopaminergic receptors, relax renal and mesenteric vessels without influence on

cardiac function. Moderate doses of dopamine (5–20 mg/kg in 1 minute) stimulate β_1-adrenergic receptors of the heart that leads to the increase of cardiac output and heart rate. Renal blood flow is also increased. Blood pressure does not change significantly. Administration of high doses of drug (more than 20 mg/kg in 1 minute) results in excitation of α-adrenergic receptors. Resistance of renal vessels, peripheral vascular resistance, and blood pressure are incresed. Heart rate and force of cardiac contraction are increased too. Dopamine can provoke cardiac arrhythmia. Dopamine does not penetrate central nervous system. The drug is administered intravenously drop-by-drop to treat shock of different genesis.

Angiotensinamide is amide of natural angioconstrictor angiotensin II. Vasoconstrictive effect of angiotensinamide is 40 times greater than those of noradrenaline. Hypertensive effect of angiotensinamide is due to excitation of angiotensin receptors of arterioles. Wherein, venous tone is increased insignificantly. Vessels of internal organs (especially kidneys) and skin are the most sensitive to angiotensinamide. The drug practically does not directly influence heart and its circulation.

Angiotensinamide stimulates aldosterone synthesis that leads to sodium and water retention in the body. Owing to this, extracellular fluid volume and blood pressure are increased. Besides, angiotensinamide increases adrenaline release, stimulates vasomotor centre, improves transmission through sympathetic ganglia, and increases peripheral effects of noradrenaline.

The drug is administered intravenously drop by drop to treat acute arterial hypotension. Tachyphylaxis does not develop to angitensinamide. Its possible side effects are headache, allergic reactions, renal vasoconstriction, etc.

At hypotension with hypovolemia, therapeutic effect is achieved by means of administration of blood, plasma, or plasma expanders. These agents are especially effective at hemorrhage and body dehydration. Simultaneously, antiaggregants and anticoagulants are administered.

Frontline treatment of shock includes administration of drugs stimulating α-adrenergic receptors *(norepinephrine, mesatonum, etilefrine), dopamine,* or *angiotensinamide*. The administration of epinephrine with this aim is possible but inadvisable, because stimulation of β-adrenoceptors is accompanied by vasodilation of some vascular regions and hypertensive effect is less expressive. Also, it should be noticed that marked cardiostimulatory effect of adrenaline is dangerous in patients with coexisting ischaemic heart disease.

To treat different forms of arterial hypotension, the drugs of choice are *midodrine* and *etilefrine (phethanolum).* In comparison with other drugs (*mesatonum, caffeine,* etc.) these drugs have longer effect.

Pharmacology of groups 1, 2, 3.1, 3.2, 3.3, 3.6, and 4 is given in corresponding chapters.

Table 3 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
Hygronium	Intravenously drop-by-drop 0.04–0.08 g (as 0.1 % solution in isotonic NaCl solution)	Ampoules 0.1 g of powder for injection
Pentaminum	Intramuscularly 0.05–0.1 g; intravenously slowly 0.01–0.025 g (in 10–20 ml of isotonic solution of NaCl solution)	Ampoules 1 or 2 ml of 5 % solution
Benzohexonium	Orally 0.1–0.2 g 3–6 times a day; subcutaneously or intramuscularly 0.025 g 1–2 times a day	Tablets 0.1 g; ampoules 1 ml of 2.5 % solution
Tropaphenum	Subcutaneously or intramuscularly 0.01–0.02 g; intravenously slowly 0.01 g in 10–20 ml of isotonic NaCl solution	Ampoules 0.02 g of powder for injection

Continuation of the table 3

Drug name (Latin)	Single dose and mode of administration	Drug product
Anaprilinum	Orally 0.01–0.04 g; intravenously slowly 0.001 g	Tablets 0.01 or 0.04 g; ampoules 1 or 5 ml of 0.1 % solution
Metoprololum	Orally 0.05–0.1 g	Tablets 0.05 or 0.1 g
Prazosinum	Orally 0.000 5–0.002 g	Tablets 0.001, 0.002 or 0.005 g
Octadinum	Orally 0.025–0.05 g	Tablets 0.025 g
Reserpinum	Orally 0.000 05–0.000 1 g	Tablets 0.000 1 or 0.000 25 g
Clophelinum	Orally 0.000 75–0.000 15 g; subcutaneously or intramuscularly 0.000 05–0.000 1 g; intravenously 0.000 05–0.000 1 g in 10–20 ml of isotonic NaCl solution	Tablets 0.000 075 or 0.000 15 g; ampoules 1 ml of 0.01 % solution
Methyldophum	Orally 0.25 g	Tablets 0.25 g
Phenigidinum	Orally 0.01–0.02 g	Tablets 0.01 g
Diazoxidum	Intravenously 0.075–0.3 g	Ampoules 20 ml (0.3 g)
Magnesii sulfas	Intramuscularly or intravenously slowly 1–5 g	Ampoules 5, 10 or 20 ml of 20 % or 25 % solution
Captoprilum	Orally 0.025–0.05 g	Tablets 0.025 g
Losartanum	Orally 0.1 g	Tablets 0.1 g
Dichlothiazidum	Orally 0.025–0.05 g	Tablets 0.025 or 0.1 g
Furosemidum	Orally 0.04 g; intramuscularly or intravenously 0.02 g	Tablets 0.04 g; ampoules 2 ml of 1 % solution
Spironolactonum	Orally 0.025–0.05 g	Tablets 0.025 g
Noradrenalini hydrotartras	Intravenously drop-by-drop 0.004–0.008 g in 1 *l* of isotonic NaCl solution	Ampoules 1 ml of 0.2 % solution
Mesatonum	Orally 0.01–0.025 g; subcutaneously or intramuscularly 0.003–0.005 g; intravenously 0.001–0.003 g in 10–20 ml of isotonic sodium chloride solution, or intravenously drop-by-drop	Powders; ampoules 1 ml of 1 % solution

Step 1. Tasks for Self-Control
Antihypertensive and Hypertensive Drugs

1. A 58-year-old female has undergone surgery for bowel necrosis. Despite having been treated with antibiotics, on postoperative day 5, she develops symptoms (fever, hypotension, tachycardia, decreased urine output, and confusion) consistent with septic shock. What haemodynamic support would be helpful?

A. Antibiotic administration.
B. Fluid and dobutamine infusion.
C. Atropine administration.
D. Fluid administration.
E. Dobutamine infusion.

2. In a hypertensive patient who is taking insulin to treat diabetes, which of the following drugs is to be used with extra caution and advice to the patient?

A. Methyldopa.
B. Prazosin.
C. Octadine (guanethidine).
D. Anaprilinum.
E. Hydralazine.

3. Drugs that block catecholamine uptake process (e. g., cocaine, tricyclic antidepressants) are apt to block the antihypertensive action of which of the following drugs?

A. Diazoxide.
B. Propranolol.
C. Prazosin.
D. Hydralazine.
E. Guanethidine.

4. Point out nonselective β-adrenergic blocking agent that is also a competitive antagonist at α_1-adrenoceptors.

A. Labetalol.
B. Nadolol.
C. Pindolol.
D. Acebutolol.
E. Timolol.

5. A 35-year-old female with pheochromocytoma is treated with labetalol. Select the mechanism of labetalol action.

A. Mixed α- and β-antagonist.

B. α-Adrenergic antagonist.

C. β-Adrenergic agonist.

D. β-Adrenergic antagonist.

E. α-Adrenergic agonist.

6. A 65-year-old male has a blood pressure of 170/105 mmHg. Which of the following would be effective in lowering this patient's blood pressure?

A. Scopolamine.

B. Prazosin.

C. Dobutamine.

D. Proserinum.

E. Terbutaline.

7. A 66-year-old male with a one-year history of essential hypertension has minimal response to diet and diuretic. His blood pressure is now 160/105 mmHg. The diuretic is discontinued, and propranolol is given. Select the mechanism of action that is associated with propranolol.

A. β-Adrenergic agonist.

B. α-Adrenergic antagonist.

C. M-cholinergic agonist.

D. Sodium channel antagonist.

E. β-Adrenergic antagonist.

8. A patient has a hypertensive emergency with blood pressure of 210/140 mm Hg. Which of the following drugs would be most effective intravenously?

A. Atropine.

B. Pirilenum (pempidine).

C. Pachycarpine.

D. Arfonad (trimethaphan).

E. Scopolamine.

9. ACE inhibitors are associated with a high incidence of which of the following adverse reactions?

A. Hirsutism.

B. Proteinuria.

C. Agranulocytosis.

D. Hepatitis.

E. Hypokalaemia.

10. Point out antihypertensive drug producing marked relaxation of smooth muscle of both venules and arterioles.

A. Sodium nitroprusside.

B. Anaprilinum.

C. Octadine.

D. Reserpine.

E. Verapamil.

11. A 50-year-old male with a two-year history of essential hypertension well controlled on dichlothiazide is found on a recent physical examination to have a blood pressure of 160/105 mm Hg. Dichlothiazide is substituted with another agent. Two weeks later, he returs for follow-up complaining of a taste loss. Select the drug which is most likely to have caused this adverse effect.

A. Propranolol.

B. Adenosine.

C. Captopril.

D. Nifedipine.

E. Furosemide.

12. A 54-year-old female is treated for essential hypertension with an antihypertensive drug that controls her blood pressure. One day, she comes to the emergency department with chest pain, tachycardia, anxiety, and blood pressure of 240/140 mm Hg. She has not taken her medication for two days. Which antihypertensive drug can account for her findings?

A. Prazosin.

B. Propranolol.

C. Doxazosin.

D. Minoxidil.

E. Clonidine.

13. A 48-year old salesman with known hypertension complains of a decreasing annual income, a loss of “drive”, and a depressed

outlook on life. His blood pressure is normal on medication. What is the antihypertensive drug being most likely to be the cause of his new complaints?

A. Reserpine.

B. Methyldopa.

C. Hydralazine.

D. Hydrochlorothiazide.

E. Guanethidine.

14. Clonidine hydrochloride lowers blood pressure by reducing sympathetic tone. It is believed to act by inhibiting sympathetic outflow from the vasomotor centre in the medulla. What is a potentially serious adverse reaction that has been reported?

A. Systemic lupus erythematosus.

B. Anaphylaxis.

C. Irreversible nephrotoxicity.

D. Ventricular fibrillation.

E. Withdrawal syndrome resembling hypertensive crisis.

15. Diuretic drug was prescribed to the patient with hypertension in the course of complex treatment. In a few days blood pressure decreased but signs of hypokalaemia developed. What drug could cause such complications?

A. Triamterene.

B. Lasix.

C. Spironolactone.

D. Enalapril.

E. Clophelinum.

16. A patient with hypertensive disease with accompanying obstructive bronchitis receives anaprilinim (propranolol) in complex therapy. After a while, the attacks of asthma become more frequent. What is the cause of this side effect?

A. Stimulation of bronchial α_1-adrenoceptors.

B. Blockade of bronchial β_1-adrenoceptors.

C. Blockade of bronchial β_2-adrenoceptors.

D. Blockade of bronchial α_2-adrenoceptors.

E. Stimulation of bronchial β_2-adrenoceptors.

17. For the correction of arterial pressure in collaptoid state mesatonum has been injected to the patient. What is the mechanism of this drug action?

A. Stimulation of α- and β-adrenoceptors.

B. Stimulation of β-adrenoceptors.

C. Blockade of β-adrenoceptors.

D. Blockade of α-adrenoceptors.

E. Stimulation of α_1-adrenoceptors.

18. A patient suffers from hypertensive crisis. What is it necessary to prescribe to the patient for normalization of the arterial pressure?

A. Propranolol.

B. Magnesium sulfate.

C. Prazosin.

D. Atropine.

E. Reserpine.

19. High renin level is developed in blood of 55-year-old patient with hypertensive disease. What hypotensive drug should be prescribed for the treatment of the patient?

A. Prazosin.

B. Clophelinum.

C. Enalapril.

D. Papaverine.

E. Magnesium sulfate.

20. Antihypertensive agent has decreased the blood pressure during first several days of treatment owing to diminish of minute heart volume. In four weeks of using, minute heart volume restored to initial level, but blood pressure had remained low. Indicate drug which is used in this case.

A. Losartan.

B. Prazosin.

C. Methyldopa.

D. Octadine.

E. Anaprilinum.

21. A 65-year-old patient received the injection of drug A. for interruption of hypertensive crisis. It is known, that drug A. has

anticonvulsive and analgesic actions; and in case of peroral administration it also shows the laxative and bile-expelling actions. Identify drug A.

A. Magnesium sulfate.

B. Sodium nitroprusside.

C. Clophelinum.

D. Pentaminum.

E. Dibazole.

22. A patient with hypertensive crisis was admitted to the cardiological department. He was given an intravenous injection of an antihypertensive drug – alkali-earth metal salt. What drug was injected?

A. Potassium chloride.

B. Sodium hydrocarbonate.

C. Calcium lactate.

D. Benzohexonium.

E. Magnesium sulfate.

DRUGS TO TREAT ISCHAEMIC HEART DISEASE (ANTIANGINAL DRUGS)

Antianginal drugs eliminate the imbalance between myocardial oxygen demand and oxygen delivery to the heart. Due to this, drugs arrest angina attacks and relief progression of ischaemic heart disease. According to data of WHO, frequence of ischaemic heart disease elevated more than 10 times during last 40 years. Tendency to increase is mainly kept at the expense of 35–40-year-old people. There are several clinical forms of ischaemic heart disease: angina pectoris, myocardial infarction, atherosclerotic cardiosclerosis, etc.

Antianginal drugs are classified as follows.

1. Drugs decreasing myocardial oxygen demand and improving supply of oxygen to a heart.

1.1. Organic nitrates: *nitroglycerin, nitrosorbidum (isosorbide dinitrate), isosorbide mononitrate, erynitum, sustac mite, sustac forte, trinitrolong, nitrong.*

1.2. Calcium channel antagonists: *verapamil, gallopamil, nifedipine, nicardipine, amlodipine, diltiazem, nisoldipine*.

1.3. Potassium channel activators: *nicorandil, pinacidil*.

1.4. Different drugs: *amiodarone, molsidomine*.

2. Drugs decreasing myocardial oxygen demand.

2.1. β-adrenoceptor antagonists: *anaprilinum, nadolol, oxprenolol, metoprolol, talinolol, nebivolol, acebutolol*.

2.2. Bradicardiac drugs (sinus node inhibitors): *ivabradine, alinidine, falipamil*.

3. Drugs increasing oxygen delivery to myocardium.

3.1. Myotropic coronary vasodilating drugs: *carbocromen, dipyridamole, papaverine, No-spa*.

3.2. Coronary vasodilating drug with reflex action: *validolum*.

4. Cardioprotective drugs: *trimetazidine (Preductal), ATP-long,* antioxidants and antihypoxants (*emoxypine (Mexidol), Oliphen, Ubinonum)*.

It should be noticed that treatment of ischaemic heart disease is complex and necessarily includes, besides antianginal agents, drugs of other groups: tranquilizers, antiaggregants, anticoagulants, vitamins, anabolics, hypolipidemic drugs, etc.

The main antianginal drugs are organic nitrates, calcium channel antagonists, and β-adrenergic antagonists.

Drugs Decreasing the Myocardial Oxygen Demand and Improving the Myocardial Blood Supply

Organic Nitrates

Nitroglycerin was implemented in medicine in 1876. Take into account its efficacy and frequency of clinical use, nitroglycerin is the main antianginal drug down to here. Different nitroglycerin-containing drugs and some other organic nitrates are used nowadays to treat ischaemic heart disease. Organic nitrates are effective at all forms of angina pectoris – effort angina, Prinzmetal's (variant) angina, postinfarction angina, progressive angina pectoris.

It is known that myocardial oxygen demand is determined by heart work. In turn, heart work depends from heart rate, force of cardiac contraction, preload, and afterload. Preload is determined by the degree of pressure in ventricles at the end of diastole (depends on venous return). Afterload is determined by blood pressure level in the aorta (depends on peripheral resistance).

Vasodilation, caused by nitrates, is occurred by means of NO-groups acting analogically endothelial relaxing factor. It is known that in patients suffering from ischaemic heart disease the production of endothelial relaxing factor is reduced due to lesions of arterial wall endothelium.

Organic nitrates interact with sulfhydryl groups of cysteine which is a part of nitrate receptors located in membranes of endotheliocytes. An interaction of nitrates with HS-groups of cysteine leads to the S-nitrosocysteine synthesis and the release of NO_2 which is transformed in NO. Nitric oxide diffuses into the cells of vascular smooth muscles where stimulates guanylyl cyclase that leads to the increase of cGMP level. cGMP by means of cGMP-dependent protein kinase influence smooth muscles contraction, reducing calcium intracellular concentration. It results in dephosphorylation of myosin light chains and smooth muscle relaxation. Besides, nitrates stimulate synthesis of prostaglandins and suppress thromboxane A_2 synthesis, that leads to the decrease of adhesion and aggregation of platelets and improves microcirculation. Low doses of nitrates dilate veins, whereas high nitrate doses also relax arteries.

Besides peripheral action, nitrates also exhibit expressive central action. Drugs decrease adrenergic influence upon heart and vessels that also promotes vasodilatation.

The main factor of anti-ischaemic effect of nitrates is their ability to decrease venous blood return to heart due to the dilation of capacitive vessels and blood deposition in them that is accompanised by the reduction of cardiac preload. Reduction of arterioles tone is less expressive but also useful because results in the decrease of cardiac afterload.

Decrease of both preload and afterload leads to the reduction of heart work and reduction of myocardial oxygen demand.

Improvement of coronary blood flow is a secondary consideration. But unlike other coronarolytics, nitrates dilate large coronary arteries that promotes to increase of perfusion pressure at the entrance to sclerous segments of vessels. Therefore, nitrates increase blood velocity in the ischaemic area. Steal phenomenon is uncharacteristic of nitrates.

It is necessary to note, that redistribution of intracardial blood flow is in favor of the most vulnerable subendocardial sections.

Also, nitrates dilate vessels of brain, internal organs, and retina. Because nitrates are myotropic antispasmodics, they relax smooth muscles of internal organs (gastrointestinal tract, bronchi, etc.).

The used medicinal forms of nitrates determine the routes of drugs administration, speed of effect development, and duration of antianginal action. If a drug is used to prevent angina attacks, speed of its effect development is not critical. But it is determinative factor in case when a drug is used to arrest angina attacks. A number of medicinal forms of *nitroglycerin* for sublingual administration are used to arrest stenocardia attacks: tablets, alcoholic and oil solutions (dosed by drops), spray for irrigation of mouth, and capsules. These medicinal forms are used only sublingually because nitroglycerin is destroyed at first passage through the liver. Also, there is medicinal form of nitroglycerin for intravenous administration.

At sublingual administration, nitroglycerin avoids the first passage through the liver. Drug is readily absorbed into superior vena cava system and enters systemic blood circulation. The bioavailability of sublingual nitroglycerin is more than 90 %. It should be notised that nitroglycerin absorption significantly depends on intensity of salivation. At dry mouth, bioavailability of nitroglycerin is significantly reduced. Therefore, nitroglycerin spray is preferable to use in patients with disorders of salivation.

At sublingual administration, maximum concentration of nitroglycerin in the blood is observed in 2–3 minutes. Nitroglycerin

effect lasts 15–20 minutes and is determined by active metabolit of nitroglycerin – dinitroglycerin. In 20–30 minutes, only trace of drug is observed in the blood. Nitroglycerin undergoes hepatic biotransformation by conjugation with glutathione. Its metabolites are excrated through the liver and lungs.

Medicinal forms with slowly release *nitroglycerin* are used to prevent angina attacks. These drugs are special microcapsulated forms containing granules of nitroglycerin with different velocity of absorbtion. These drugs are prescribed from 1 to 3–4 times a day. Nitroglycerin sustained-release forms include tablets "*Sustac mite*" and "*Sustac forte*", polymer plates "*Trinitrolong*". There are transdermal forms of nitroglycerin: ointment and plaster discs with nitroglycerin. Therapeutic effect of transdermal nitroglycerin develops slowly and lasts 8–24 hours.

Group of nitrates with prolonged action includes *nitrosorbidum*, *isosorbide mononitrate*, and *isosorbide dinitrate*. The efficacy of these drugs is less than those of nitroglycerin.

Nitrates are used to arrest and to prevent angina attacks. Also, drugs are administered intravenously drop-by-drop to treat myocardial infarction in acute period.

Postural hypotension is the most dangerous complication of nitrate therapy. Other side effects of nitrates include reflex tachycardia, increased intracranial and intraoccular pressure, headache, feeling the heat, and hyperemia of the face. Cases of hemorrhagic stroke also are described. Tolerance develops approximately in 58 % of patients who regularly take nitroglycerin during 1.5–2 months. To prevent tolerance, nitrate-free period of 10–12 hours duration (overnight) is needed.

Sudden phasing out of long-time nitrate intake leads to rebound phenomenon. It is characterized by increased intensively of chest pain and increased frequency of angina attacks. Rebound phenomenon can result in myocardial infarction and sudden death. Therefore, phasing out of nitrate intake should be done by gradually reducing the drug dose and the frequency of its intake.

It is necessary to notice that long-time intake of nitrates can provoke methemoglobinemia.

Calcium Channel Blockers (Calsium Antagonists)

Calcium channel blockers are classified as follows:

– calcium channel blockers, 1st generation: *verapamil, nifedipine, diltiazem*;

– calcium channel blockers, 2nd generation: *gallopamil, amlodipine, felodipine, nicardipine, nisoldipine*;

– calcium channel blockers, 3rd generation: *naftopidil, emopamil*.

According to chemical structure, calcium channel blockers are divided into 3 subgroups:

– phenylalkylamine derivatives: *verapamil, gallopamil*;

– dihydropyridine derivatives: *nifedipine, nicardipine, nisoldipine, isradipine, felodipine, amlodipine*;

– benzothiazepine derivatives: *diltiazem, clentiazem*.

In comparison with the first-generation, the second-generation drugs are characterized by longer duration of action and higher selectivity to calcium channels of certain localization. Third-generation calcium antagonists are drugs with additional properties: *naftopidil* exhibits α-adrenoblocking activity, *emopamil* – sympatholytic activity. All three generations exhibit antianginal, antiarrhythmic, and antihypertensive activity.

Calcium channel blockers inhibit calcium entrance through L-type slow calcium channels into the muscular cells of vessels and heart. A decrease of free calcium ions concentration in the cardiac histiocytes leads to reduction of energy consumption of ATP for mechanical work of myocardium. A force of the heart contractions decreases that results in reduction of myocardial oxygen consumption. Decreased heart work is also a result of relaxation of peripheral arteries and reduction of afterload. Dilation of coronary vessels also promotes the antianginal effect, because it improves myocardial oxygen delivery. Besides, calcium antagonists improve the subendocardial blood flow and collateral circulation.

Also, calcium antagonists inhibit platelet aggregation and release of thrombocytic biologically active substances which induce vasospasm and increase blood clotting.

Calcium channel blockers are taken orally or sublingually and administered parenterally. Drugs are completely (more than 90 %) and rapidly absorbed from the gastrointestinal tract. But drugs undergo first-pass elimination in the first passage through the liver. Bioavailability of calcium channel blockers is about 35 % (for *nifedipine, nitrendipine,* and *amlodipine* it varies from 65 to 90 %). About 90 % dose reaching systemic circulation binds with plasma proteins. Calcium antagonists readily penetrate various tissues and organs including central nervous system. Duration of action of first-generation drugs is 4–6 hours. Second-generation calcium channel blockers act 12 hours. Almost 100 % of administered dose of calcium antagonists are metabolized by liver with the formation of inactive metabolites. Only metabolites of *verapamil* and *diltiazem* exhibit some pharmacological activity. Metabolites of calcium channel blockers are excreted mainly by kidneys (80–90 %) and partly – by liver.

Calcium channel blockers are used to treat all types of angina (variant angina and effort angina). Derivatives of phenylalkylamine and benzothiazepine are predominantly used in the treatment for angina with coexisting supraventricular tachycardia. Dihydropyridine derivatives are used to treat angina which is accompanied by bradycardia, disorders of atrioventricular conduction, or arterial hypertension.

Besides, calcium antagonists are used in the treatment for hypertensive disease, supraventricular tachyarrhythmias, atrial flutter, atrial fibrillation, and to prevent cold-induced bronchospasms.

Side effects of calcium channel blockers are headache, dizziness, arterial hypotension, flushing (as a rule at nifedipine intake), constipations, bradycardia (for phenylalkylamine derivatives) or tachycardia (for dihydropyridine derivatives).

Potassium Channel Activators

This group includes *nicorandil* and *pinacidil*. Potassium channel activators open ATP-sensitive potassium channels and promote potassium ions outflow from the smooth muscle cells that leads to membrane hyperpolarization and reduces vascular tone.

Pinacidil dilates both peripheral and coronary vessels and decreases afterload. The drug's administration is accompanied by reflex tachycardia. Besides, pinacidil decreases the blood level of cholesterol and triglycerides. Its side effects are headache, tachycardia, hypertrichosis, etc. Pinacidil is used to treat angina pectoris and heart failure.

Nicorandil activates potassium channels and increases the synthesis of NO (nitrate-like action). Its administration leads to relaxation of coronary, resistance, and capacitance vessels, thereby both preload and afterload are reduced. Nicorandil's action is accompanied by reflex tachycardia. Drug is used in the treatment for effort angina, vasospastic angina, acute myocardial infarction, chronic heart failure, and hypertensive disease. Side effects are headeche, tachycardia, and dyspepsia.

Different Antianginal Drugs Which Both Decrease the Myocardial Oxygen Demand and Improve the Blood Supply

This group includes *amiodarone* and *molsidomine*.

Amiodarone exhibits antianginal and antiarrhythmic effects. Its mechanism of action is associated with blockage of potassium, calcium, and sodium channels. Besides, amiodarone exhibits β- and α-adrenergic blocking activity. Also, amiodarone is antagonist of glucagon. Therefore, amiodarone slows down heart rate and decreases blood pressure. Consequently, myocardial oxygen demand is decreased. Also, amiodarone improves coronary circulation.

Amiodarone is taken orally or administered intravenously slowly. Degree of its absorption from gastrointestinal tract is approximately 50 %. Amiodarone undergoes hepatic biotransformation. Its metabolites are excreted mainly by intestine.

Drug is used to prevent angina pectoris attacks, to prevent and to treat both supraventricular and ventricular tachyarrhythmias. Marked therapeutic effect of amiodarone develops in several weeks after treatment initiation.

Long-time amiodarone therapy may be accompanied by deposition of microcrystals of the drug in the cornea, skin pigmentation, photodermatoses, thyroid dysfunction, bradycardia, and hypotension.

Molsidomine (Corvaton) undergoes hepatic metabolism with formation of active metabolite releasing NO. Nitric oxide is strong vasodilator and, therefore, is also called "endothelium-derived relaxing factor". Molsidomine selectively relaxes peripheral veins, decreases adhesion and aggregation of thrombocytes, and increases the elasticity of large arteries. Molsidomine decreases both cardiac preload and afterload, reduces myocardial oxygen demand, and increases coronary circulation. Unlike nitrates, long-time molsidomine intake does not lead to tolerance, because the drug does not interact with HS-groups of proteins.

Molsidomine is administered parenterally, sublingually, and taken orally. Gastrointestinal absorption of molsidomine is about 60 %. Drug does not bind with plasma proteins. At oral intake, the drug effect develops in 20–30 minutes. Sublingually taken molsidomine begins to act in 5 minutes. Duration of molsidomine action is 6–8 hours. Biotransformation of molsidomine occurs in liver. Metabolites of molsidomine undergo renal and hepatic excretion.

Molsidomine is used both to treat and to prevent angina pectoris attacks. Besides, the drug is used in the tretment for chronic and acute heart failure, myocardial infarction, and hypertension. Its side effects are headache, hyperemia of the face, nausea, muscular spasms, etc.

Drugs Decreasing Myocardial Oxygen Demand

β-Adrenoceptor Antagonists

β-adrenoceptor antagonists are the main drugs in therapy of majority of cases of ischaemic heart disease.

Depending on selectivity to certain types of β-adrenergic receptors, β-adrenergic antagonists are classified as follows:

1) β_1 and β_2-adrenoceptor antagonists (nonselective β-adrenoceptor antagonists): *anaprilinum (propranolol), nadolol, sotalol, oxprenolol,* and *pindolol*;

2) β_1-adrenoceptor antagonists (cardioselective β-adrenoceptor antagonists): *metoprolol, talinolol, atenolol, nebivolol, acebutalol,* etc.

The drugs decrease excessive influence of stress and negative emotions upon cardiovascular system due to blockage of β_1-adrenergic receptors in the heart. Under the influence of β-adrenoceptor antagonists, the force of cardiac contractions and heart rate are decreased that leads to reduction of myocardial oxygen demand.

It should be noticed that β-adrenoceptor antagonists negatively influence coronary circulation due to blockage of β_2-adrenergic receptors of coronary vessels (for nonselective drugs) and reduction of stroke volume and cardiac output. Therefore, high efficacy of β-adrenoceptor antagonists in ischaemic heart disease is the result of pronounced reduction of myocardial oxygen demand.

Long-time (during months and years) therapy by individually selected doses of β-adrenoblockers decreases in 2 (and more) times frequancy of sudden death of patients with ischaemic heart disease and postinfarction patients, improves patients' state, increases exercise tolerance, significantly decreases frequancy and severity of angina attacks.

Generally, cardioselective β-adrenoceptor antagonists are preferable in the treatment for ischaemic heart disease because these drugs do not block vascular β_2-adrenergic receptors and, thus, reduce of coronary and peripheral circulation in less degree. Besides, unlike

$\beta_{1,2}$-adrenergic antagonists, these drugs insignificantly increase risk of bronchoconstriction at concomitant pathology of respiratory organs.

β-Adrenergic antagonists with intrinsic sympathomimetic activity (pindolol, etc.) reduce myoacardial contractile activity in less degree, therefore these drugs are preferable in the treatment for ischaemic heart disease for patients with symptoms of heart failure and for posinfarction patients.

β-adrenoceptor antagonists are taken orally and administered pareneterally. Most drugs are readily (70–90 %) absorbed from gastrointestinal tract. Bioavailability of β-adrenoceptor antagonists is nearly 50 %. Biotransformation of drugs occurs in the liver. Degree of binding with plasma proteins for different drugs varies from 5 to 90 %. Duration of action for majority of drugs is approximately 8 hours; for metoprolol – 12 hours; for atenolol and pindolol – 24 hours. Lipophilic β-adrenoceptor antagonists are excreted mainly by the liver; hydrophilic ones – by the kidneys.

Most commonly, β-adrenoceptor antagonists are used to treat effort angina in patients with tendency to increase blood pressure and heart rate. Usually, cardioselective β-adrenoceptor antagonists are used together with drugs of other groups. β-adrenoceptor antagonists with intrinsic sympathomimetic activity (e. g., pindolol) are preferable for treatment of patients with concomitant bradycardia and with hidden symptoms of heart failure.

Also, β-adrenoceptor antagonists are used in the for treatment for hypertensive disease, supraventricular tachyarrhythmisas, extrasystoles, thyrotoxicosis, and to prevent repeated myocardial infarction.

Side effects of β-adrenoceptor antagonists are bradycardia, conduction disorders, arterial hypotension, heart failure, bronchoconstriction, worsening of lipid spectrum (drugs increase the level of atherogenic lipoproteins), central nervous system suppression, hypoglycemia, vasospasm of limbs, and dyspeptic disorders.

It should be noticed that therapy by β-adrenergic antagonists is not accompanied by tolerance. These drugs keep their efficacy at longstanding intake. But sudden cessation of β-adrenoceptor antagonist intake can result in serious aggravation of ischaemic heart disease up to myocardial infarction. Therefore, discontinuation of the drug intake should be gradual.

Bradicardic Drugs

Bradicardic drugs are *alinidine, ivabradine,* and *falipamil*. These drugs significantly decrease heart rate and myocardial oxygen demand. Bradycardia is due to direct suppressive influence of drugs upon automatism of sinus node (drugs slow down phase of diastolic depolarization). Besides antianginal action, bradicardic drugs also exhibit antiarrhythmic effect. Drugs don't influence circulatory dynamics.

Ivabradine is the most studied representative of this group. The drug blocks I_f-channels that leads to reduction of Na^+ and K^+ inward current into the cells of sinus node. Therefore, ivabradine slows down diastolic depolarization and decreases automatism of sinus node. Simultaneously, blood supply of endocardium is improved. The drug does not influence myocardial contractility and conduction. Ivabradine is used to treat ischaemic heart disease and chronic heart failure. The drug is taken two times a day. Ivabradine does not cause rebound syndrome.

Drugs Increasing Oxygen Delivery to Myocardium

Coronary Vasodilating Drugs with Myotropic Action

This group includes drugs which dilate coronary vessels and eliminate coronary spasm (e. g., *dipyridamole, papaverine).*

Dipyridamole (Curantyl) influences myocardial microcirculation, because it decreases the tone of small resistance vessels owing to inhibition of reuptake of adenosine by cardiac histiocytes and erythrocytes. Drug also inhibits the activity of adenosine deaminase. It is known, that adenosine is released in

hypoxia of myocardium and causes marked dilation of coronary arteries. Also, dipyridamole suppresses the platelets aggregation and improves microcirculation. The drug does not change the systemic peripheral resistance. Dipyridamole is used to prevent angina attacks for patients without atherosclerotic lesions. It is necessary to note, that in patient with coronary atherosclerosis, dipyridamole does not improve oxygen delivery to ischaemic area. Moreover, the drug can worsen blood circulation in ischaemic region. It is explained by the fact that in ischaemic area small coronary vessels are relaxed in maximum degree (compensatory reaction). After dipyridamole administration, small vessels are relaxed also in non-ischaemic regions of myocardium. It promotes the reduction of blood circulation in ischaemic area. This phenomenon is called steal syndrome. This effect of dipyridamole is sometimes used to determine latent coronary insufficiency.

Dipyridamole is taken orally and administered parenterally. Side effects are headache, dyspepsia, hypotension, etc.

Papaverine is alkaloid of opium. Drug exhibits low coronary vasodilating activity and has short duration of action. Mechanism of action is associated with inhibition of phosphodiesterase that leads to increase of intracellular cAMP concentration. Increase of cAMP concentration results in reduction of calcium concentration in vascular smooth muscles and elevation of calcium level in cardiac histiocytes. Therefore, relaxation of coronary vessels is accompanied by increase of cardiac contraction force. Simultaneously, papaverine insignificantly inhibits reuptake of adenosine by cardiac histiocytes. Besides, papaverine decreases systemic arterial pressure, reduces the cerebrovascular tone, and relaxes the smooth muscles of inner organs. Papaverine has a limited use to prevent angina attacks.

Antianginal Drugs with Reflex Action

Validolum is 25–30 % menthol solution in menthol ether of isovaleric (3-methylbutanoic) acid. Drug is taken sublingually to interrupt slight angina attacks. Menthol irritates the cold receptors in oral cavity that leads to reflex relaxation of coronary vessels. The antianginal activity of validolum is low. If in 2–3 minutes after the drug intake pain is not arrested, validolum should be replaced by nitroglycerin.

Cardioprotective Drugs

Trimetazidine (Preductal, Vastarel) directly influences cardiac histiocytes in ischaemic area and normalizes their energy balance. It is not accompanied by changes of total hemodynamics. It is expected that trimetazidine's mechanism of action is associated with inhibition of 3-ketoacyl-CoA thiolase that leads to reduction of fatty acid oxidation. Against this background, glucose oxidation is activated that favourably influences myocardial function. Trimetazidine is taken 3 times a day. Preductal MB is prolonged medical form which is taken 2 times a day. Trimetazidine is readily absorbed from gastrointestinal tract, undergoes hepatic biotransformation, and excreted by kidneys. The drug is well tolerated by patients.

Adenosine triphosphate (ATP) participates in different metabolic processes. At interaction with actomyosin, it degrades to ADP and inorganic phosphate. This process is accompanied by release of energy which is used for the cardiac work and anabolic processes. Besides, ATP is considered as one of the mediators of adenosine receptors. In patients with ischaemic heart disease, ATP concentration in myocardium is decreased. Administration of ATP increases cerebral and coronary blood circulation. Value of exogenous ATP is questionable, because significant amount of energy is necessary for penetration of ATP across the cell membranes. Therefore, special medical form – ATP-long – was

approved. It plays the role of coordinating drug: ATP together with potassium, magnesium, and histidine penetrate inside of cardiac histiocytes. Intracellular ATP provides anti-ischaemic and antiarrhythmic affects.

Special drugs to reduce cardiac hypoxia – antihypoxants – are used in medicine. Antioxidants hold a high positin between antihypoxants. These drugs exhibit antiradical effect and inhibit lipid peroxidation. These drugs include such agents as *emoxypine* (*Mexidol*), *ubinone* (*ubiquinone*), *oliphen*, etc.

Principles of Complex Therapy of Myocardial Infarction

Myocardial infarction is acute disease developing due to occurrence of one or more foci of heart muscle necrosis in result of absolute or relative coronary circulation deficiency. In most cases, the main cause of myocardial infarction is atherosclerosis of coronary vessels (it is registered in 90 % of died from infarction). Usually, myocardial infarction is accompanied by severe pain, fear of death, excitement, sharp activation of the sympathoadrenal system, spasm of the coronary and peripheral arteries. It creates additional load upon the heart and increases the conflict between oxygen delivery to myocardium and its oxygen demand. In 90 % cases, myocardial infarction is accompanied by cardiac arrhythmias and acute heart failure, which can lead to ventricular fibrillation and cardiogenic shock. All medical measures in myocardial infarction should be held whithin short timeframes. A patient needs bed regime.

Opioid analgesics (*phentanyl, morphine, promedol, tramadol,* etc.), tranquilizers (*diazepam*), and neuroleptics (*droperidol,* on the condition that blood pressure is not decreased) are administered to relief pain and to eliminate death anxiety and excitement. If painful syndrome is not reduced, opioid analgesic is administered again in 20–30 minutes. If it is necessary, inhalation nitrous oxide with oxygen is given to patient. It should be noticed

that analgesia by metamizole (analgin) and diphenhydramine (dimedrol) is, as a rule, ineffective.

Nitroglycerin or *isosorbide dinitrate* are administered intravenously drop-by-drop to unload the heart. The earlier these drugs are administered the higher is their effectiveness. It is necessary to notice, that nitrates' administration is contraindicated at collapse and shock.

β-adrenoceptor antagonists are administered to decrease the heart work and to reduce tachycardia. Selective β_1-adrenoceptor antagonists (*metoprolol* or *talinolol*) are preferable. These drugs are prescribed for initial intravenous administration with the further their oral intake.

To prevent or eliminate ventricular tachyarrhythmias, *lidocaine* or *amiodarone* are administered.

To support cardiac contractile function, cardiac glycosides are used seldom, because they can provoke dangerous arrhythmias against the background of ischaemia. *Dopamine* or *dobutamine* are preferable cardiotonics for this aim. These drugs are administered intravenously drop-by-drop. At danger of pulmonary oedema, dopamine is administered together with nitroglycerin. Also, infusion of glucose with insulin is used to maintenance of the heart trophism.

Fibrinolytics (*streptokinase, urokinase, alteplase,* etc.) are used to eliminate coronary thrombosis. These drugs lyse thrombi and restore coronary circulation. To prevent further thrombosis, anticoagulants (*heparin, fraxiparine,* etc.) are administered. Antiaggregants (*aspirin, clopidogrel, ticlopidine*) are prescribed as early as possible.

Inhaled oxygen is used during all period of acute myocardial infarction therapy. Hyaluronidase is used to increase vascular permeability in ischaemic area. Antioxidants (*α-tocopherol, emoxypine,* etc.) and glucocorticoids are prescribed to suppress inflammation.

Table 4 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Nitroglycerinum	Sublingually 0.000 5 g at an attack of angina pectoris (it is necessary previously to get to the core of a capsule by teeth); intravenously drop-by-drop 0.000 5–0.00 1 g (concentration of administered solution is 0.01 % or 100 mcg / ml)	Tablets 0.000 5 g; capsules 0.000 5 g of 1 % oil solution; ampoules 10 ml of 0.1 % solution, 2 ml of 0.5 % solution, and 2 ml of 1 % solution
Isosorbide mononitrate	Orally 0.02–0.04 g 2–4 times a day	Tablets 0.02 or 0.04 g
Sustac mite	Orally 1 tablet 2 times a day	Tablets containing 2.6 mg nitroglycerin
Sustac forte	Orally 1 tablet once a day	Tablets containing 6.4 mg nitroglycerin
Validolum	Sublingually 0.05–0.06 g at an attack of angina pectoris	Tablets 0.06 g; capsules 0.05 g
Anaprilinum	Orally 0.01–0.04 g 3 times a day; intravenously slowly 0.001 g in 10–20 ml of 0.9 % NaCl solution	Tablets 0.01 or 0.04 g; ampoules 1 or 5 ml of 0.1 % solution
Amiodaronum	Orally 0.2 g 1–2 times a day; intravenously slowly 0.005 g/kg in 10–20 ml of 0.9 % NaCl solution 1–3 times a day	Tablets 0.2 g; ampoules 3 ml of 5 % solution
Verapamilum	Orally 0.04–0.08 g 3 times a day; intravenously slowly 0.005–0.01 g in 10–20 ml of 0.9 % NaCl solution	Tablets 0.04 or 0.08 g; ampoules 2 ml of 0.25 % solution
Amlodipinum	Orally 0.005–0.01 g 1 time a day	Tablets 0.005 or 0.01 g

Step 1. Tasks for Self-Control
Drugs to Treat Ischaemic Heart Disease (Antianginal Drugs)

1. Therapy with anaprilinum (propranolol) has positively affected the course of the disease of a 44-year-old woman with angina pectoris. What is the mechanism of antianginal action of this drug?

A. Decrease of the need for oxygen and increase of the coming of oxygen into the myocardium.

B. Decrease of the oxidative exchange in the myocardium due to the inhibition of Krebs cycle enzymes.

C. Decrease of myocardium energy consumption due to the decrease of load.

D. Increase of oxygen coming into the myocardium.

E. Inhibition of β_1-adrenoceptors and decrease of the myocardium need for oxygen.

2. Bronchlospasm was developed in patient with angina pectoris after taking of antianginal drug. What drug could provoke this effect?

A. Nifedipine.

B. Propranolol.

C. Sustac forte.

D. Dipyridamole.

E. Nitroglycerin.

3. Anaprilinum (propranolol) therapy caused positive effect in the dynamics of the disease of 44-year-old woman suffering from stenocardia. What is the main mechanism of this drug effect?

A. Decrease of oxidative exchange in myocardium due to enzyme blockade of Krebs cycle.

B. Increased oxygen supply to the myocardium.

C. Decreased power inputs of myocardium due to reduced loading.

D. Decreased need in increasing of oxygen supply to the myocardium.

E. Blockade of β-adrenoceptors and decrease of myocardial requirements to the oxygen.

4. A 48-year-old patient after severe psychoemotional exertion suddenly began feeling sharp pain in the heart region, irradiating into left arm. Nitroglycerin relieved pain 10 minutes later. What pathogenetic mechanism is responsible for the development of pain in this case?

A. Occlusion of coronary vessels.

B. Compression of coronary vessels.

C. Dilation of peripheral vessels.

D. Spasm of coronary vessels.

E. Increase of myocardial needs in oxygen.

5. A patient after tooth extraction developed persistent substernal pain. Sublingual antianginal substance relieved the pain, but the patient complained of headache and dizziness. What medicine did the patient use?

A. Metoprolol.

B. Validol.

C. Nytroglycerin.

D. Verapamil.

E. Anapriline.

6. A patient with acute myocardial infarction was given intravenously different solutions during 8 hours with medical dropper 1 500 ml and intranasall oxygen. He died because of pulmonary oedema. What caused pulmonary oedema?

A. Neurogenic reaction.

B. Inhalation of the oxygen.

C. Volume overload of the left ventricular.

D. Decreased oncotic pressure due to haemodilution.

E. Allergic reaction.

7. Therapeutic action of β-adrenergic receptor blockers such as anaprilinum (propranolol) in angina pectoris is believed to be primarily the result of:

A. Increased sensitivity to catecholamines.

B. Dilation of the coronary vasculature.

C. Reduced production of catecholamines.

D. Increased peripheral resistance.

E. Decreased requirement for myocardial oxygen.

8. Which of the following drugs is considered to be most effective in relieving and preventing ischaemic episodes in patients with variant angina?

A. Isosorbide dinitrate.

B. Nifedipine.

C. Sustac-mite.

D. Propranolol.

E. Nitroglycerin.

9. A 69-year-old male with angina develops severe constipation following treatment with:

A. Nitroglycerin.

B. Captopril.

C. Propranolol.

D. Verapamil.

E. Dobutamine.

10. Administration of which of the following antianginal agents results in antianginal effects for only 10 hours, despite detectable therapeutic plasma levels for 24 hours?

A. Transdermal nitroglycerin.

B. Atenolol.

C. Amlodipine.

D. Validolum.

E. Verapamil.

11. A 70-year-old female is used nitroglycerin for for sublingual intake to interrupt angina pectoris attacks. Point out process which is involved in the mechanism of nitroglycerin action.

A. Excitation of β-adrenergic receptors.

B. Inhibition of phosphodiesterase.

C. Excitation of α-adrenergic receptors.

D. Inhibition of norepinephrine release.

E. Increase of cGMP concentration.

12. Which of the following is unlikely to occur with low concentrations of nitroglycerin?

A. Increased coronary blood flow.

B. Decreased end-diastolic blood pressure.

C. Decreased myocardial oxygen demand.

D. Decreased preload and afterload.

E. Decreased heart rate.

13. A 61-year-old female has intermittent bouts of chest pain on exertion of two months' duration, associated with numbness and tingling in the fourth and fifth fingers of her left hand. ECG is normal. She is placed on anaprilinum (propranolol), which relieves her symptoms. What cardiovascular effect has this drug?

A. It increases sensitivity to catecholamines.

B. It dilates the coronary vasculature.

C. It decreases production of catecholamines.

D. It decreases the requirement for myocardial oxygen.

E. It increases peripheral vascular resistance.

14. A patient comes to your office with effort-induced angina and resting tachycardia. You choose the following drug to treat the patient because it slows heart rate by blocking L-type calcium channels in SA node.

A. Metoprolol.

B. Verapamil.

C. Nitroglycerin.

D. Isosorbide dinitrate.

E. Propranolol.

15. Which of the following haemodynamic effects of nitroglycerin are primarily responsible for the beneficial results observed in patients with angina?

A. Increased blood flow to the subepicardial layer.

B. Reduction in systemic vascular resistance (afterload).

C. Reduction in preload.

D. Reduction in the force of myocardial contraction.

E. Increased heart rate.

16. A combination of drugs, consisting of nitroglycerin patch and β-blocker, such as propranolol, is prescribed to woman to treat her attacks of angina. Which effect of propranolol would counteract adverse effect of nitroglycerin?

A. Reduction in coronary vasospasm.

B. Decrease in afterload.

C. Decrease in preload.

D. Increase in myocardial contractile force.

E. Decrease in heart rate.

17. Metoprolol would produce the following beneficial effect in a patient with angina:

A. Increase in diastolic filling time.

B. Increase in collateral blood flow.

C. Increase in afterload.

D. Decrease in preload.

E. Increase in blood flow through concentric stenosis.

18. A doctor recommended to patient, who had an acute myocardial infarction, to take acidum acetylsalicylicum in the dose 0.25 g once per 2–3 days during 3–4 months. What effect did the doctor count on?

A. Antiaggregant.

B. Anti-inflammatory.

C. Antipyretic.

D. Analgesic.

E. Vasodilative.

19. A patient with ischaemic heart disease has not informed the doctor that he had attacks of bronchospasm. The doctor prescribed a drug, which has made the attacks of angina pectoris less frequent, but the attacks of bronchospasm have become more frequent. What drug has been prescribed?

A. Nitrosorbidum (isosorbide dinitrate).

B. Atenolol.

C. Propranolol (anaprilinum).

D. Diltiazem.

E. Verapamil.

20. A patient has been suffering from bronchial asthma for a long time. Recently he had attacks of angina pectoris. What drug is contraindicated to him?

A. Dipyridamole.

B. Nitroglycerin.

C. Sustac forte.

D. Propranolol.

E. Nifedipine.

21. A 53-year-old woman suffers from attacks of angina pectoris. The patient suffers from severe chest pain, arrhythmia, and short breath. What drug is the most expedient for prescription in this case to provide first aid?

A. Amiodarone.

B. Nitrosorbidum.

C. Nitroglycerin.

D. Sustac forte.

E. Propranolol.

22. A doctor has prescribed hypolipidemic drug to patient with ischaemic heart disease. It is known, that this drug predominantly decreases the level of triglycerides in the blood. What drug was prescribed to the patient?

A. Nicotinic acid.

B. Fenofibrate.

C. Glybenclamide.

D. Insulin.

E. Prednisolone.

23. A patient with acute stenocardia attack is delivered to hospital. What drug should be administered to patient for interruption of angina pectoris attack?

A. Calcium chloride.

B. Vicasolum.

C. Heparin.

D. Nitroglycerin.

E. Furosemide.

24. A doctor has diagnosed acute attack of stenocardia which is accompanied by tachyarrhythmia and hypertension in 60-year-old patient. It is known, that this patient also suffers from diabetes mellitus and bronchial asthma. The doctor administered intravenously some antiadrenergic drug to patient. Identify this drug.

A. Octadinum.

B. Anaprilinum.

C. Phentolamine.

D. Reserpine.

E. Metoprolol.

25. A patient suffering from bronchial asthma began to feel chest pain. Indicate the antianginal drug which is contraindicated to this patient.

A. Isoptin (verapamil).

B. Corinfar (nifedipine).

C. Nitrosorbide.

D. Anaprilinum.

E. Sustac forte.

26. A patient suffering from coronary artery disease had taken a certain drug many times a day in order to arrest stenocardia attacks. Overdose of this drug finally caused intoxication. Objectively: cyanotic skin and mucous membranes, dramatic fall in the arterial pressure, tachycardia, and respiration inhibition. Blood has increased concentration of methemoglobin. The drug that was taken by patient relates to the following group:

A. α-Adrenoceptor blockers.

B. Organic nitrates.

C. Myotropic spasmolytics.

D. Adenosine drugs.

E. Calcium channel blockers.

ANTIARRHYTHMIC DRUGS

Cardiac arrhythmias are disorders of frequency, rhythmicity, or sequence of excitation and contraction of heart's compartments. Depending on localization of pathological focus, arrhythmias are divided into supraventricular, atrioventricular, and ventricular ones. There are tachyarrhythmias (extrasystoles, paroxysmal tachycardia, flutter and fibrillation of atriums or ventricules) and bradyarrhythmias (different types of blockades, sick sinus syndrome). Ventricular arrhythmias are most dangerous and require urgent care.

Direct reasons of rhythm disorders are quite varied. But, obviously, local disorders of electrolyte balance are most common causes of arrhythmias. Deficite of K^+ and Mg^{2+} or excessive concentration of Na^+ and Ca^{2+} develop in myocardium due to hypoxia, inflammation, toxic or autoimmune lessions, increased sympathetic tone, excessive concentration of thyroid hormones, etc.

Graphically, process of formation of action potential is as follows.

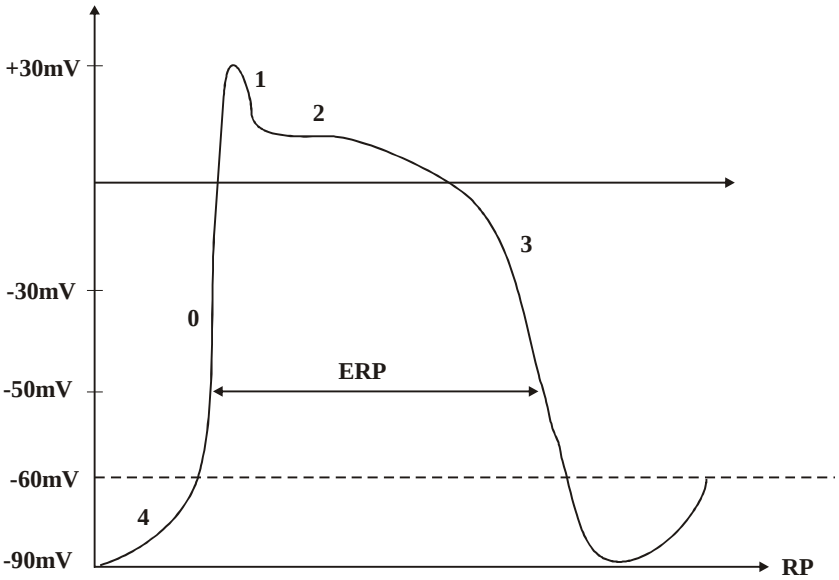

Figure 1 – *Action potential of cardiac histiocytes and sinus node:*

4 – phase of spontaneous (slow) diastolic depolarization;
0 – phase of rapid depolarization;
1 – phase of initial (early) repolarization;
2 – plateau;
3 – rapid repolarization;
RP – resting potential;
ERP – effective refractory period

This action potential is the result of activation and inactivation of multiple ion channels, which allows the flow of charged ions

across the membrane. The ions flow through open channels according to the electrochemical driving forces at any given moment.

Physiological pacemaker is sinus node located in the wall of right atrium. From it, impulses carried out to atrioventricular node, then – bundle of His and its left and right branches, and then – Purkinje fibers. The mentioned structures form cardiac conductive system, through which impulses come to muscular fibeds of ventricles.

Cells of sinus node are able to spontaneous slow depolarization (phenomenon of automatism) during diastole (phase 4). At normal physiological state, automatism of other parts of conduction system is inhibited by sinus node and is less expressive. In sinus node, phase 4 is associated with penetration of Ca^{2+} (and insignificant amount of Na^{+}) through slow Ca^{2+} channels in pacemaker cells during diastole. When critical level of membrane potential is achived, fast ionic channels opened and permeability of cellular membrane for Na^{+} and Ca^{2+} is sharply increased. Excitation wave spreads to adjacent membrane sections. It is phase of rapid depolarization (phase 0). After phase 0, repolarization begins. Early repolarization (phase 1) is due to transient outward current of K^{+} ions. During plateau (phase 2), ions of Ca^{2+} and Na^{+} enter the cell, but, simultaneously, K^{+} ions come out of the cell. Phase 3 (rapid repolarization) is result of Na^{+}, K^{+}-ATPase activity which restores initial ratio of ions' concentration inside and outside of the cell (pumps Na^{+} out of the cell and K^{+} - into the cell). Alongside, calcium ATPase pumps excessive Ca^{2+} ions out of the cell.

During phases 0, 1, and 2, cardiac cells are transiently unresponsive to any activation stimuli. This time is called absolute refractory period. Only at the end of phase 3, stimule of increased force can cause cellular excitation. Time from the start of action potential to moment, when new cellular excitation become possible, is called effective refractory period. Refractoriness is protective mechanism from excessively-fast repeated excitation which can affect cardiac contractile function.

Speed of diastolic depolarization of cardiac histiocytes and conduction system depends on activity of vegetative nervous system. Activation of sympathetic nervous system and stimulation of adrenergic receptors increase cellular membrane permeability for calcium and sodium ions that accelerates spontaneous diastolic depolarization. Increased parasympathetic tone, activation of M-cholinergic and purinergic receptors is accompanied by outflow of potassium ions and membrane hyperpolarization that deccelerates spontaneous diastolic depolarization and decreases heart rate.

Antiarrhythmic drugs are classified as follows:

1) drugs which are used to treat tachyarrhythmias:

a) membrane stabilizing drugs (sodium channel blockers, or class I according to classification of Vaughan–Williams – one of the most widely used classification scheme of antiarrhythmic drugs):

– subgroup IA: *quinidine sulfate, novocainamidum (procainamide), disopyramide,* and *ajmaline;*

– subgroup IB: *lidocaine, trimecaine,* and *dipheninum (phenytoin);*

– subgroup IC: *flecainide, propafenone, aetmozinum (moracizine),* and *ethacizine*.

b) β-adrenoceptor antagonists (class II): *anaprilinum (propranolol), pindolol, talinolol, metoprolol, atenolol.*

c) drugs increasing the duration of action potential (class III): *amiodarone, ornidum (bretylium),* and *sotalol*.

d) calcium channel blockers (class IV): *verapamil* and *diltiazem*.

e) drugs which selectively inhibit Na^+ and K^+ iflux in sinus node cells (bradycardiac drugs): *falipamil, alinidine,* and *ivabradine*.

f) miscellaneous antiarrhythmic agents:

– potassium- and magnesium-containing drugs: *potassium chloride, Asparcamum, Panangin;*

– *adenosine*;

– cardiac glycosides: *digoxin*.

2) drugs which are used to treat bradyarrhythmias:

a) adrenergic agonists: *epinephrine (adrenaline), isadrinum (isoprenaline),* and *ephedrine*.

b) M-cholinoceptor antagonists: *atropine,* etc.

c) hormonal drugs: *glucagon*.

Drugs Used to Treat Tachyarrhythmias

Membrane Stabilizing Drugs (Blockers of Sodium Channels, Class I)

Drugs of Class IA

Membrane stabilizing drugs reduce permeability of cellular membrane for sodium ions through "slow" sodium channels of ectopic focuses of automatism, therefore these drugs inhibit speed of spontaneous depolarization of sodium type (phase 4). Besides, these drugs inhibit sodium permeation through "fast" channels (phase 0) and outward potassium current during repolarization (phase 2) that leads to prolongation of effective refractory period. Due to this, duration of refractory period in ectopic focus are aligned with those in unchanged myocardial regions. Quinidine-like drugs prolong the duration of P–Q interval, QRS complex, and QT interval of ECG. Membrane stabilizing drugs inhibit contractile function of left ventricle and decrease blood pressure. Against the background of administered quinidine and disopyramide, heart rate is accelerated due to blockage of M-cholinergic receptors. Mentioned drugs promote atrioventricular conduction.

Quinidine is alkaloid of Cinchona bark. Initially, it was used as antimalarial agent. The drug is taken mainly orally, sometimes – administered intravenously. The last route of administration is used seldom owing to danger of significant hypotension and development of heart failure. At oral intake, quinidine's bioavailability is 44–89 %, that is determined by different velocity of its biotransformation at first passage through the liver. The degree of binding with plasma proteins is about 70–80 %. At oral intake, onset of the drug action is 1–2 hours, duration – 8 hours. Quinidine is taken 3–5 times a day. The main route of drug excretion is kidneys. Quinidine is used to treat supraventricular and ventricular tachyarrhythmias. The drug exhibits maximum efficacy at supraventricular arrhythmias, especially paroxysmal atrial tachycardia and auricular flutter and fibrillation. Side effects of quinidine are dyspepsia, exacerbation of heart failure, hypotension,

visual disorders, headache, tinnitus, thrombocytopenia, diminished hearing, hepatotoxicity, photosensitization, and lupus-like syndrome.

Novocainamidum (procainamide) is a derivative of the local anaesthetic agent novocainum (procaine). The drug is administered parenterally (intramuscularly or intravenously) and taken orally. Procainamide is readily absorbed from gastrointestinal tract. Its bioavailability is about 85 %. A degree of binding with plasma proteins is 15–20 %. About 70 % administered dose is metabolized in the liver. Unchanged procainamide and its acetylated metabolites are excreted mainly by kidneys. The drug is taken 4–6 times a day. Procainamide inhibit myocardial contractility in less degree than quinidine. The drug is most effective at ventricular tachyarrhythmias (extrasystoles, paroxysmal ventricular tachycardia). Procainamide is not used to treat chronic forms of arrhythmias. Its side effects are dyspepsia, hypotension, (less than at quinidine's use), systemic lupus erythematosus, agranulocytosis, myalgia, arthralgia, etc. Fast intravenous administration can provoke collapse and convulsions.

Disopyramide (Rytmilen) is taken orally or administered parenterally (intramuscularly and intravenously). The drug is readily absorbed from gastrointestinal tract. Its bioavailability is 70–85 %; the degree of binding with plasma proteins is 20–30 %. Disopyramide acts 4–5 hours, therefore the drug is taken 3–4 times a day. About 50 % administered dose undergoes hepatic biotransformation. The drug and its metabolites are excreted by kidneys. Disopyramide is used to treat ventricular extrasystoles, paroxysmal supraventricular and ventricular tachycardia; to prevent arrhythmias during surgical operations on the heart and large vessels. Side effects of disopyramide are mainly due to its M-cholinoblocking activity: dry mouth, accommodation disorders, increased intraocular pressure, tachycardia, and dyspepsia. Sometimes, the drug can cause agranulocytosis and photosensitization. Disopyramide significantly suppressed cardiac contractility.

Ajmaline (Arytmal) is alkaloid of *Rauvolfia serpentina*. The drug is administered parenterally and taken orally. Ajmaline is badly

absorbed from gastrointestinal tract; its binding with plasma proteins is insignificant. The drug is almost completely metabolized in the liver; its metabolites are excreted by kidneys. Ajmaline is prescribed 3–6 times a day. The drug is used to treat ventricular tachyarrhythmias only. The following side effects are observed at the drug intake: dyspepsia, hypotension, asystolia, cirrhosis-like changes of liver, cholestasis, and disorders of cardiac conduction.

Drugs of Class IB

Members of class IB block Na^+ channels (mainly in phase 4) and increase membrane permeability for K^+ ions facilitating their ouflax from the cells. These drugs influence Purkinje fibers and cardiac histiocytes in ventricles. The drugs of IB class shorten phase 2 of membrane repolarization. These agents decrease the duration of effective refractory period and action potencial. An increase of duration of P–Q interval and QRS complex is observed on ECG. Drugs of IB class decrease duration of QT interval. These drugs do not affect practically left ventricle contractility and blood pressure.

Lidocaine is administered intramuscularly, intravenously drop-by-drop, or taken orally. But its gastrointestinal bioavailability is less than 30 % due to significant biotransformation at first passage through the liver. About 10–40 % administered dose of lidocaine binds with plasma proteins and acid glycoproteins. Long-time infusion of lidocaine is often accompanied by complications, because toxic metabolites are synthesized due to its biotransformation. Lidocaine is drug of choice to treat and to prevent ventricular arrhythmias at myocardial infarction, in postoperative period, at implantation of electric cardiac pacemaker, and glycoside intoxication. As a rule, the drug is well tolerated by patients. Side effects of lidocaine are hypotension, drowsiness, vertigo, weakness, nervousness, numbness of tongue and lips. Chemical structure and pharmacological properties of *trimecaine* are similar to lidocaine.

Dipheninum (phenytoin) is taken orally and, sometimes, administered intravenously. Its gastrointestinal absorption is slow, but bioavailability is high – 98 %. About 87–93 % administered dose

binds with plasma proteins. The drug is metabolized in the liver practicly completely (about 90 % administered dose). Metabolites are excreted mainly by kidneys and partly – by liver. Dipheninum is effective only at ventricular arrhythmias (especially due to glycosides overdose). The drug is able to improve atrioventricular conduction. Dipheninum exhibits antiarrhythmic action against the background of hypokalemia and does not suppress cardiac contractile function. Its side effects include neurological disorders (ataxia, disartria, increased nervousness or lethargy), fever, and difficulty in breathing. Large doses of dipheninum can provoke bradycardia, hypotension, and gum hypertrophy.

Drugs of class IC

Mechanism of action of IC class drugs is similar to those of of class IA. These drugs influence all compartments of the heart decreasing membrane permeability for Na^+ ions and slowing down diastolic depolarization (phase 4). It should be noticed that these drugs do not influence membrane permeability for K^+ ions (phase 2). On ECG, drugs of IC class prolong duration of P–Q interval and QRS complex. Duration of QT interval is not changed. These drugs decrease myocardial contractile function and blood pressure.

Aetmozinum (moracizine) is taken orally and administered intravenously drop-by-drop. Its gastrointestinal bioavailability is about 38 %. Less than 10 % administered dose binds with plasma proteins. The drug effect develops is 10–20 min. after intravenous administration and in 2–3 days in case of oral intake. Aetmozinum is practicly completely metabolized in liver; its metabolites are excreted by kidneys. Aetmozinum is used to treat severe ventricular tachyarrhythmias arising against background of angina pectoris. Also, the drug is used in the treatment for atrial fibrillation and atrial flutter. Typical side effects of aetmozinum is associated with its ability to block M-cholinergic receptors and include dry mouth, tachycardia, and difficulty urinating. Besides, the drug can cause dizziness, stomach pain, skin itch, and numbness of tongue.

Ethacizine is administered intravenously and taken orally. The drug is readily absorbed from gastrointestinal tract, but its bioavailability is only about 40 % because significant amound of the drug is inactivated at first passage through the liver. Little amount of administered dose is bonds with plasma proteins. At intravenous administration, the drug effect develops in 10–15 min., at oral intake – in 1–2 days. Inactive metabolites of ethacizine are excreted by kidneys. The drug is used to treat ventricular and supraventricular tachyarrhythmias. Its side effects are nausea, numbness of tongue, dizziness, disorders of accommodation. Intravenous drug administration can cause tinnitus, numbness of different body parts, and mesh before eyes. It should be noticed that ethacizine exerts M-choliblocking activity and increases heart rate.

Besides mentioned above antiarrhythmic mechanism, *propafenone* exhibits weak β-adrenoblocking activity and inhibits calcium channels. Unlike ethacizine, propafenone slows down heart rate. The drug is administered intravenously or taken orally. At oral intake, tablet cannot be chewed because the medicinal remedy causes superficial anaesthesia and has marked bitter taste. The drug bioavailability is 50 %. At oral intake, effect develops in 1 hour and lasts 6–7 hours. Propafenone degree of binding with plasma proteins is about 95 %. The drug is excreted brom the body by the kidneys and liver. The drug is taken 4 times a day to treat ventricular and supraventricular tachyarrhythmias against myocardiodystrophy, valvular heart disease, etc. Side effects of propafenone include decreased contractile myocardial function, atrioventricular blockage, sinus dysfunction, and dyspepsia.

β-Adrenoceptor Antagonists

Group of β-adrenoceptor antagonists is represented by such drugs as *anaprilinum (propranolol), oxprenolol, pindolol, metoprolol, talinolol, atenolol,* etc. Their mechanism of action is associated with blockage of cardiac β_1-adrenoceptors that eliminates arrhythmogenic influence of of catecholamines. Besides,

some drugs (e. g., propranolol) influence calcium and sodium inward current in phases 4 and 0 (quinidine-like membrane stabilizing effect). But, this effect is appreciable only if drugs are administered in large doses and has secondary importance in diapason of usual therapeutic doses. β-Adrenoblockers decreased oxygen myocardial demand and, therefore, eliminate hypoxia and associated with it metabolic and electrolyte disorders and dysfunction of cellular membranes. These drugs somewhat accelerate exit of K^+ ions and shorten phase 2 decreasing effective refractory period. Owing to the decrease of catecholamines influence upon diastolic depolarization, β-adrenergic antagonists inhibit sinus node automatism and activity of ectopic pacemakers. β-Adrenoblockers slow down conduction through atrioventricular node. Prolongation of P–Q interval is observed on ECG. Sedative influence of these drugs upon central nervous system is also important.

β-Adrenergic antagonists are used to treat supraventricular and ventricular tachyarrhythmias which caused by high sympathoadrenal tone (neurogenic or hormonal disorders of rhythm, initial period of myocardial infarction, etc.). Intravenously administered propranolol is rescue medication at paroxysmal rhythm disorders.

Inhibition of contractile myocardial function (up to heart failure) is one of the most serious side effects of β-adrenoblockers. Therefore, administration of β-adrenergic antagonists is dangerous in acute period of myocardial infarction with symptoms of heart failure. Besides, these drugs can cause atrioventricular blockage. Due to blocking of β_2-adrenoceptors, nonselective β-adrenergic antagonists (propranolol, oxprenolol, nadolol, etc.) can provoke bronchospasm, disorders of blood circulation in extremities, headache, etc. As a rule, selective β_1-adrenoblockers (metoprolol, talinolol, atenolol, etc.) do not cause such side effects.

Drugs Slowing Down Repolarization

Amiodarone (Cordarone) is most interest drug of this group. The drug exhibits broad spectrum of antiarrhythmic activity. Amiodarone blocks K^+ channels and slows down repolarization in phase 3, prolongs action potential, and significantly increases duration of effective refractory period. Besides, amiodarone exerts moderate blocking activity concerning Na^+ channels, α- and β-adrenergic receptors. Also, the drug weak inhibitor of Ca^{2+} channels. By means of blockage of glucagon receptors, amiodarone eliminates its stimulating influence upon the heart. Duration of QT and P–Q intervals is increased.

Amiodarone is taken orally or administered intravenously. The drug is poorly absorbed from gastrointestinal tract and undergoes biotransformation in the liver and in intestinal wall. Its gastrointestinal bioavailability is 20 %. The degree of binding with plasma proteins is more than 90 %. Amiodarone and its metabolites are excreted by liver. The drug is prescribed one time a day. At oral intake, amiodarone effect develops is 1–2 weeks and lasts 15–20 days after phasing out of the drug.

Amiodarone is used to treat supraventricular and ventricular tachyarrhythmias and effort angina.

Long-time amiodarone therapy leads to sedimentation of yellow brown micro-crystals in the cornea which disappeared after cessation of the drug intake. Other side effects of amiodarone include dyspepsia, headache, athaxia, paresthesia, thyroid dysfunction (molecules of amiodarone contain iodine), diffuse interstitial pneumonia, pulmonary fibrosis, gray-blue skin coloration, and hepatocellular necrosis.

Bretylium (ornidum) slows the inward current of Ca^{2+} in phase 2 of action potential. Besides, the drug exerts sympatholytic properties by reducing of catecholamine release from presynaptic nervous endings. Bretylium is administered intramuscularly and intravenously. The drug is not absorbed from gastrointestinal tract. At intramuscular administration, antiarrhythmic effect develops

in 30 minutes and lasts 12 hours. Bretylium is excreted by kidneys in unchanged form.

Bretylium is used in the treatment for ventricular tachyarrhythmias, especially during acute period of myocardial infarction and in cases refractory to lidocaine. Its side effects include hypotension, hot feeling, nausea, oedema of nasal mucosa, temporary visual disorders, etc. Sometimes, necrosis develops in the site of intramuscular injection.

Medical drug *sotalol* consists of *l*- and *d*-isomers. *l*-Sotalol is nonselective blocker of β-adrenergic receptors; *d*-sotalol inhibits potassium channels. Due to this mechanism, sotalol prolongs repolarization. Also, sotalol inhibits sinus automatism, slows dows conduction, and causes bradycardia. The drug is easily absorbed from gastrointestinal tract. Its bioavailability is 90–100 %. The main route of its excretion is kidneys. Sotalol is used to treat ventricular and supraventricular tachyarrhythmias. The drug is taken 2 times a day. Its side effects are bradycardia, decrease of contractile myocardial function, fatigue, etc.

Nowadays, number of new drugs, inhibiting potassium, channels and prolonging effective refractory period, are used in medicine. *Dofetilide (Tikosyn)* is one of them. The drug inhibits potassium channels and prolongs repolarization. Also, dofetilide causes mild bradycardia. The drug is easily absorbed from gastrointestinal tract; its bioavailability is about 90 %. Dofetilide is partly heptic metabolized by liver and excreted by kidneys. The drug is used to treat supraventricular tachyarrhythmias. It should be noticed that dofetilide exerts proarrhythmogenic action and can cause ventricular tachyarrhythmias and conduction disorders. Besides, the drug can cause such side effects as chest pain and dizziness.

Calcium Channel Blockers (Class IV)

Verapamil and *diltiazem* block slow calcium channels of L-type. These drugs affect inward calcium current and slow down Ca^{2+}-dependent depolarization (phase 4, and partly – phase 0) in sinoatrial and atrioventricular nodes. Thus, the drugs inhibit automatism and slow down atrioventricular conduction. Practically, calcium channel blockers do not influence Purkinje fibers. Duration of P–Q interval is increased. Calcium antagonists reduce contractile myocardial function, heart rate, and blood pressure.

Verapamil is most commonly used calcium channel blocker to treat arrhythmias. The drug is administered intravenously or taken orally. Oral bioavailability of verapamil is about 20 %. Its degree of binding with plasma proteins is 90 %. Verapamil and its metabolites are excreted with urine (about 80 %) and bile. The drug is taken 3–4 times a day. Verapamil is used to treat supraventricular tachyarrhythmias (paroxysmal tachycardial and atrial fibrillation) and angina pectoris. Its side effects are hypotension, exacerbation of heart failure, atrioventricular blockage, dyspepsia, constipation, headache, fatigue, and swelling in the legs.

Diltiazem exerts less expressive antiarrhythmic activity. At oral intake, its effect develops in 30 minutes and lasts 6 hours. Diltiazem is metabolized by liver and excreted by intestine. Its side effects are identical to those of verapamil.

Miscellaneous Antiarrhythmic Agents

This group includes *potassium chloride*, *Asparcamum*, *Panangin*, *adenosine*, and digitalis glycosides.

Adenosine is nucleotide synthesized due to degradation of ATP. Adenosine acts as mediator of purinergic synapses and as local hormone. Adenosine interacts with adenosinergic receptors of A_1–A_4 types which, through G-proteins, stimulate or inhibit adenylyl cyclase. The drug slows down atrioventricular conduction and inhibits contractile myocardial function (influence upon A_1-receptors), dilates coronary vessels and decreases platelets aggregation (influence upon A_2-receptors). Besides, adenosine

increases bronchial tone (through A_1-receptors), stimulates the release of biologically active substances from basophils (interaction with A_3-receptors), and inhibits central nervous system.

Adenosine is administered intravenously. Its duration of action is about 30 seconds. The drug is used to terminate supraventricular tachyarrhythmias. Wherein, its effect is associated with inhibition of atrioventricular conduction. Side effects of adenosine are breathing disorders, short-time atrioventricular blockage, face redness, etc. it should be noticed that antagonists of adenosine are methylxantines (caffeine, theophylline).

Potassium-containing drugs (*potassium chloride, Asparcamum, Panangin, polarizing mixture*) are used at arrhythmias accompanied by reduction of potassium concentration in plasma and in myocardium: glycoside intoxication, atrial fibrillation, ventricular extrasystolia, myocardial infarction, etc.). Potassium ions influence myocardium like acetylcholine: decrease heart rate, inhibit conduction, automatism, and excitability. Low concentrations of K^+ ions dilate coronary vessels, but high concentrations cause coronary vasoconstriction. Potassium drugs are taken orally and administered intravenously. Overdose of potassium leads to paresthesies, dyspepsia, atrioventricular blockage, and renal dysfunction.

Magnesium drugs (*magnesium sulfate, magnesium orotate, magnesium aspartate*) also exert antiarrhythmic activity. These drugs are aspecially effective at hypomagnesaemia. Magnesium drugs are used in the treatment for ventricular tachycardia and fibrillation.

Digoxin is cardiac glycoside which used to treat supraventricular tachyarrhythmias. The drug activity is associated with the increase of vagal tone that leads to slowing of conduction through atrioventricular node. Therefore, conduction of extremely frequance impulci to ventricles is worcened.

Drugs Used to Treat Bradyarrhythmias

Atrioventricular and sinoatrial blockages, atrial asystole, and blockage of conduction through bundle of His results in bradyarrhythmias. This pathology can develop at myocardial infarction, acute inflammation and dystrophia of myocardium, intoxications by cardiac glycosides, cholinomimetics, potassium salts, etc. Extreme case of bradyarrhythmia is attack of temporary asystole with loss of consciousness up to 5 seconds or more (Stokes–Adams attacks).

M-cholinergic Antagonists

M-cholinergic antagonist *atropine* improves automatism and conduction by means of the decrease of inhibitory vagal influence upon the heart. The drug is administered parenterally and taken orally. Atropine is easily absorbed from gastrointestinal tract. Its degree of binding with plasma proteins is about 50 %. Atropine is used to treat sinus bradycardia, sinoatrial and atrioventricular blockages, intoxications by cardiac glycosides. Its side effects are dryness of mucous membranes, constipation, tachycardia, increased intraocular pressure, disorders of accommodation, decrease of bladder tone, disorders of hit emission, etc.

Adrenomimetics

Epinephrine (adrenaline), isoprenaline (isadrinum), and *ephedrine* excite cardiac β_1-adrenoceptors that increases of automatism and facilitates conduction. Generally, these drugs are more effective than M-cholinoblockers. Isoprenaline is taken sublingually 4–6 times a day. Ephedrine is usually taken orally. At severe cases of bradyarrhythmias, isoprenaline or adrenaline are administered intravenously. It should be noticed that epinephrine is used only in crucial cases to treat bradyarrhythmias, because the drug significantly increases oxygen demand of the heart.

Glucagon

Glucagon stimulates glucagone receptors in myocardium and conductive system of the heart that increases calcium release from intracellular depot with the following increase of sinus node automatism, facilitation of conduction through atrioventricular node, and increase of myocardial contractile function. The drug is administered intravenously, sometimes – intramuscularly or subcutaneously. At intravenous administration, its effect develops in 1–4 minutes and lasts 20–30 minites.

Glucagon is used in the treatment for congestive heart failure with severe bradycardia, heart failure at full atrioventricular blockage and ventricular fibrillation, acute heart failure, cardiogenic shock, severe hypoglycemia, and poisoning by β-adrenergic antagonists, calcium antagonists, and cardiac glucosides. Therapy by glucagon may be accompanied by dyspepsia, worsening of coronary circulation, hypertensive crises, allergic reactions, decreased tone of esophageal sphincter, etc.

Severe and long-lasting bradysystole requires emergency care with the use of artificial pacemaker.

Table 5 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
Chinidini sulfas	Orally 0.1–0.3 g 2–3 times a day	Tablets 0.1 or 0.2 g
Novocainamidum	Orally, intramuscularly, or intravenously 0.25–0.5 g 1–3 times a day	Tablets 0.25 or 0.5 g; ampoules 5 ml of 10 % solution
Kalii chloridum	Intravenously drop-by-drop 2 g in 450 ml of water for injection	Ampoules 50 ml of 4 % solution
“Asparcamum” or “Pananginum”	Orally 1–2 tablets 3 times a day	Tablets containing magnesium asparaginate and potassium asparaginate
Dipheninum	Orally 0.117 g 1–3 times a day	Tablets 0.117 g

Continuation of the table 5

Drug name (Latin)	Single dose and route of administration	Drug product
Lidocainum	Intramuscularly 0.2–0.4 g; intravenously drop-by-drop 0.05–0.1 g, in the following – drop-by-drop 2 mg/min.	Ampoules 2 ml of 10 % solution and 2 or 10 ml of 2 % solution
Anaprilinum	Orally 0.01–0.04 g 3 times a day; intravenously slowly 0.001 g in 10–20 ml of 0.9 % solution of NaCl once a day	Tablets 0.01 or 0.04 g; ampoules 1 or 5 ml of 0.1 % solution
Amiodaronum	Orally 0.2 g 1–2 times a day; intravenously slowly 0.005 g/kg in 10–20 ml of 0.9 % NaCl solution 1 time a day	Tablets 0.2 g; ampoules 3 ml of 5 % solution
Verapamilum	Orally 0.04–0.08 g 3 times a day; intravenously slowly 0.005–0.01 g in 10–20 ml of 0.9 % NaCl solution	Tablets 0.04 or 0.08 g; ampoules 2 ml of 0.25 % solution

Step 1. Tasks for Self-Control
Antiarrhythmic Drugs

1. Ventricular arrhythmia followed myocardial infarction of a patient. Cardiac rhythm was normalized by the introduction of antiarrhythmic drug with local anesthesia effect. What drug was introduced?

A. Propranolol.
B. Lidocaine.
C. Verapamil.
D. Panangin.
E. Anaesthesinum.

2. A 45-year-old patient has diagnosis of ciliary arrhythmia and essential hypertension. What drug is it necessary to prescribe to this patient for prevention of arrhythmia attacks?

A. Lidocaine.

B. Sustac-forte.

C. Potassium chloride.

D. Propranolol.

E. Strophanthin.

3. A 55-year-old patient with continuing ventricular arrhythmias was admitted to the hospital. The patient is taking timolol drops for glaucoma, daily insulin injections for diabetes mellitus, and angiotensin converting enzyme inhibitor for hypertension. You decide to use phenytoin instead of procainamide. What is the reason?

A. Cholinergic effect of procainamide would aggravate diabetes.

B. Local anaesthetic effect of procainamide would aggravate the hypertension.

C. Local anaesthetic effect of procainamide would potentiate diabetes.

D. Hypertensive effect of procainamide would aggravate hypertension.

E. Anticholinergic effect of procainamide would aggravate glaucoma.

4. In patient with attacks of paroxysmal atrial tachycardia, an ideal prophylactic drug is:

A. Verapamil.

B. Procainamide.

C. Lidocaine.

D. Nifedipine.

E. Adenosine.

5. Which of the following is an antiarrhythmic agent that has relatively few electrophysiologic effects on normal myocardial tissue but suppresses the arrhythmogenic tendencies of ischemic myocardial tissues?

A. Disopyramide.

B. Lidocaine.

C. Quinidine.

D. Propranolol.

E. Procainamide.

6. A 59-year-old man with a history of rheumatic heart disease is found to have atrial fibrillation, for which he is treated with digoxin. Treatment with digoxin converts his atrial fibrillation to a normal sinus rhythm. In which of the following decrease does this treatment most likely result?

A. Sinus node automatism.

B. Speed of the cardiac muscle shortening.

C. Conduction speed in the atrioventricular node.

D. Atrial maximum diastolic resting potential.

E. Duration of the refractory period.

7. A 62-year-old patient with chronic heart failure and atrial tachyarrhythmia takes simultaneously quinidine and digoxin. If these drugs are administered concurrently, which of the following influence does quinidine have on digoxin?

A. Ability of digoxin to inhibit the Na^+, K^+-stimulated ATPase is reduced.

B. Metabolism of digoxin is prevented.

C. Absorption of digoxin from the gastrointestinal tract is decreased.

D. Effect of digoxin on the atrioventricular node is antagonized.

E. Concentration of digoxin in the plasma is increased.

8. Patients with genetically low levels of N-acetyltransferase are more prone to develop a lupus erythematosus-like syndrome with which of the following drug?

A. Lidocaine.

B. Procainamide.

C. Digoxin.

D. Captopril.

E. Propranolol.

9. The first-line drug for treating an acute attack of reentrant supraventricular tachycardia is:

A. Edrophonium.

B. Adenosine.

C. Propranilol.

D. Mesatonum.

E. Digoxin.

10. A 36-year-old male was admitted to the hospital with tachycardia, respiratory rate of 26 breaths per minute, and ECG evidence of arrhythmia. Intravenous bolus dose of antiarrhythmic agent is administered, and within 30 sec he has a respiratory rate of 45 breaths per minute and complains of a burning sensation in his chest. Select the drug most likely to have caused these adverse effects.

A. Nifedipine.

B. Digoxin.

C. Adenosine.

D. Lidocaine.

E. Dobutamine.

11. A 68-year-old female has atrial fibrillation, which is treated with antiarrhythmic agent that blocks Na^+ channels. On the recent office visit, she complained of recurrent attacks of feeling faint and of experiencing an episode of loss of consciousness. ECG should mark prolongation of the QT interval. Plasma concentration of the drug was in the therapeutic range. Select the drug most likely to have caused these adverse effects.

A. Verapamil.

B. Quinidine.

C. Bretylium.

D. Adenosine.

E. Amiodarone.

12. A 55-year-old male has recurrent ventricular arrhythmias after myocardial infarction, for which he is given an antiarrhythmic agent that blocks Na^+ channels and prolongs the action potential. One year later, a blood test is positive for circulating antinuclear antibodies. Select the drug which most likely to have caused this phenomenon.

A. Verapamil.

B. Amiodarone.

C. Adenosine.

D. Procainamide.

E. Sotalol.

13. 24 hours after an acute myocardial infarction, a 46-year-old male is being treated with a continuous intravenous drip of antiarrhythmic drug to suppress frequent multifocal premature ventricular contractions. He develops generalized seizure activity. The seizure activity can be most readily explained by:

A. Lidocaine toxicity.

B. Systemic embolization.

C. Systemic hypotension.

D. Ventricular tachycardia.

E. Ventricular asystole.

14. False statement concerning the use of calcium antagonists as antiarrhythmics:

A. They slow inward calcium current thereby decreasing the rate of spontaneous phase 4 depolarization in Purkinje fibers.

B. They slow conduction speed through the atrioventricular node and increases functional refractory period.

C. They are useful for slowing ventricular rate in atrial fibrillation.

D. Hypotension may be a limiting side effect.

E. Verapamil, diltiazem, and nifedipine exert equally effective antiarrhythmic actions.

15. Although most antiarrhythmic drugs (and indeed most drugs) are chemically synthesized, some compounds that occur endogenously in humans are useful. Indicate which of the following agents occurs endogenously and is a useful antiarrhythmic agent.

A. Lidocaine.

B. Digoxin.

C. Adenosine.

D. Quinidine.

E. Dipheninum (phenytoin).

16. Which of the following calcium channel blockers would most likely suppress atrial tachyarrhythmias involving the AV node?

A. Diltiazem.

B. Nifedipine.

C. Nicardipine.

D. Verapamil.

E. Amlodipine.

17. Point out the incorrect statements.

A. Lidocaine is used mainly for atrial arrhythmias.

B. Lidocaine must be given parenterally.

C. Procainamide is associated with a reversible lupus phenomenon.

D. Quinidine is active orally.

E. All antiarrhythmic drugs can suppress cardiac contractions.

18. Bronchoobstructive syndrome appeared in a patient during the treatment of ciliary arrhythmia. What antiarrhythmic drug can cause such complication?

A. Novocainamidum.

B. Ajmalin.

C. Nifedipine.

D. Propranolol.

E. Verapamil.

19. A patient with myocardial infarction and cardiac insufficiency has ventricular arrhythmia. What antiarrhythmic agent is a drug of choice in this case?

A. Disopyramide.

B. Quinidine.

C. Lidocaine.

D. Novocainamidum.

E. Verapamil.

20. A drug was prescribed to a 56-year-old patient who suffers from ischaemic heart disease with atrial extrasystoles. It is known, that drug blocks K^+ channels, decreases the adrenergical influence upon the heart, significantly increases the duration of action potential, and dilates the coronary vessels. What drug was prescribed?

A. Lisinopril.

B. Corglycon.

C. Nitroglycerin.

D. Dobutamine.

E Amiodarone.

21. In experiment on the heart muscle antiarrhythmic agent lowered excitability of cardiomyocytes, not influencing the action potential form. Identify this agent.

A. Amiodarone.

B. Lidocaine.

C. Verapamil.

D. Quinidine.

E. Novocainamidum.

VENOTROPIC DRUGS

Like arteries, veins are mainly innervated by sympathetic nervous system. There are α_1-, α_2- and β_2-adrenergic receptors in the smooth muscles of veins. Stimulation of α-adrenoceptors leads to constriction of veins, whereas activation of β_2-adrenoceptors results in their relaxation. Unlike regulation of arterial tone, humoral regulation of venous tone is significantly less important. Humoral regulation is realized by means of such biologically active substances as epinephrine, serotonin, histamine, kinins, angiotensin II, vasopressin, etc. Their influence may be multidirectional and depends on regulator concentration, type and initial tone of vessels, and density of corresponding receptors in membranes of smooth muscle cells. Specific mechanisms of humoral regulation upon venous tone are not understudied.

According to pharmacological effect, drugs influencing venous tone are divided into venodilators and venoconstrictors.

Venodilators are drugs which reduce venous tone. As a rule, these drugs are capable to dilate not only veins but also arteries. But influence of these drugs upon resistance and capacitance vessels is not identical. The drugs influencing mainly veins or drugs dilating veins and arteries in identical degree are used as venodilators. Such

drugs decrease cardiac preload and are used to treat ischemic heart disease, acute and chronic heart failure.

Drugs relaxing mainly veins are classified as follows.

1. Nitrous oxide donators: *nitroglycerin, nitrosorbide (isosorbide dinitrate), isosorbide mononitrate,* and *molsidomine*.

2. α-Adrenoblocking drugs: *prazosin* and *doxazosin*.

3. Sympatholytics: *octadinum (guanethidine)*.

4. Diuretics: *furosemide*.

These drugs are mainly used to treat ischemic heart disease and hypertension.

There are drugs dilating in identical degree both resistance and capacitance vessels. Their classification is follows.

1. Nitrous oxide donators: *sodium nitroprusside*.

2. Angiotensin-converting enzyme inhibitors: *captopril, enalapril,* and *lisinopril*.

3. Angiotensin receptor blockers: *losartan* and *valsartan*.

4. α_2-Adrenomimetics of central action: *clofellinum (clonidine)* and *guanfacine*.

5. Ganglionic blockers: *pentaminum (azamethonium),* benzohexonium *(hexamethonium)*.

6. $\alpha_{1,2}$-Adrenoblocking drugs: *phentolamine (regitine)*.

7. α, β-Adrenoblocking drugs: *labetalol*.

8. Phosphodiesterase inhibitors: *milrinone*.

These drugs are mainly used to treat hypertensive disease, as well as acute and chronic heart failure (angiotensin-converting enzyme inhibitors, sodium nitroprusside, milrinone, etc.).

Drugs constricting veins are classified as follows.

1. α-Adrenomimetics: *phetanol (etilefrine)* and *midodrine (Gutrone)*.

2. Alkaloids of Claviceps purpurea: *dihydroergotoxine, dihydroergotamine, dihydroergocryptine,* and *Vasobral* (*α-dihydroergocryptine* with *caffeine*).

These drugs are used in the treatment for hypotension and orthostatic collapse.

α-Adrenomimetics are drugs of synthetic origin. Phetanol provides long-lasting activation of vascular α-adrenoceptors. The drug is taken orally and administered parenterally to treat hypotensive states.

Midodrine is prodrug which is administered intravenously or taken orally. In the body, midodrine is converted into highly active metabolite desglymedodrine which exhibits α_1-adrenomimetic activity. Midodrine is used to treat hypotension and orthostatic collapse.

Alkaloids of *Claviceps purpurea* (ergot alkaloids) are agonists-antagonists of α-adrenergic receptors. Concerning arteries, these drugs exert antagonistic properties and relax them. Concerning veins, ergot alkaloids are agonists and increase their tone. Dihydroergotamine maleate and other ergot alkaloids are used to treat migraine, and disorders of blood circulation (Raynaud's disease, etc.). these drugs are administered parenterally or taken orally.

Drugs Exerting Venoprotective Properties

Chronic venous insufficiency of lower extremities is widely-spreeded circulation disorder affecting 10–40 % of population. Drugs exerting venoprotective properties and drugs exerting simultaneouly both venotonic and venoprotective properties are used to treat this pathological state.

Venoprotectors are classified as follows.

1. Drugs containing rutin and its derivatives (flavonoids): *rutin, troxerutin (Troxevasin).*

2. Drugs containing extract of *Ginkgo biloba*: *Ginkyo, Bilobil, Memoplant, Gincor fort.*

3. Synthetic drugs: *calcium dobesilate (Doxium).*

Rutin decreases permeability of small vessels, eliminates angiasthenia, improves microcirculation, and recuces oedemas. Its semisynthetic analogue troxerutin is taken orally, administered parenterally, or applied topically. The drug has long duration of action, its half-life is 24 hours. Troxerutin exerts higher toxicity than

rutin. Its side effects are gastrointestinal erosies, allergic reactions, and headache.

Drugs of *Ginkgo biloba* extract contain flavone glycosides exerting antioxidant, antioedema, and antiaggregant properties. These drugs are taken orally and easily absorbed from gastrointestinal tract.

Calcium dobesilate decreases vascular permeability and thrombocyte aggregation. At oral intake, the drug is readily absorbed from gastrointestinal tract. Its half-life is 1 hour. Side effects of calcium dobesilate are allergic reactions and dyspepsia.

Drugs Exerting both Venotonic and Venoprotective Properties

This group is classified as follows.

1. Bioflavonoids: *Detralex*.
2. Drugs obtained from horse chestnut (*Aesculus hippocastanum*) fruits: *Aescin, Reparil, Aescusan, Aesflazidum, Venoplant, Anavenol* (contains *dihydroergocryptine, aesculin*, and *rutin*).
3. Drugs obtained from *Ruscus aculeatus*: *Cyclo 3 Fort* (containing *extract of Ruscus aculeatus, hesperidin methyl chalcone*, and *ascorbic acid*).
4. Grape seed extract: *Endotelon*.
5. Synthetic drugs: *tribenoside (Glyvenol)*.

Detralex is most effective agent of this group. The drug contains two flavonoids (diosmin and hesperidin) obtained from fruits of Kumquat. The drug is taken orally 2 times a day. Detralex is metabolized by intestinal microflora to its active metabolite diosmetin. The drug increases venous tone, decreases capillary permeability, exerts anti-inflammatory effect, decreases formation of free oxygen radicals, affects platelets adhesion, improves microcirculation and lymphatic drainage, and restores tissue trophicity. Detralex is excreted from the body mainly by kidneys, partly – with bile. The drug is well tolerated by patients. Its side effects are dyspepsia, insomnia, and headache. Detralex is used to

treat chronic venous insufficiency of lower extremities and hemorrhoids.

Drugs obtained from horse chestnut fruits (*Aescin, Reparil, Aescusan,* etc.) contain triterpenoid glycosides (saponins) which exert venotonic, anti-edematous, and anti-inflammatory effects. These drugs are taken orally or applied topically. Aescusan is taken orally 3 times a day in tablets or orall drops.

Drugs of *Ruscus aculeatus* contain saponins and flavonoids. *Cyclo 3 Fort* is the most widely spreaded drug of this group. The drug is taken orally. Its typical side effect is dyspepsia.

Endotelon is drug of grape seed extract. The drug contains oligosaccharides which bind with mucopolysaccharides of venous wall. Endotelon stimulates collagen synthesis, increases venous tone, decreases venous permeability and fragility. The drug is taken orally in the treatment for first manifestations of lymphatic and venous insufficiency. Its side effects are dyspepsia, headache, skin allergies.

Synthetic drug tribenoside increases venous tone, exhibits venoprotective and capillary protective effects, inhibits inflammation, and improves microcirculation. The drug is taken orally (1 capsule 2–3 times a day), administered rectally, or applied topically. Its side effects are dyspepsia and skin rach.

Besides phlebectomy, phlebosclerosants (e. g., decilat, polidocanol) are also used to treat varicose veins. Their intravenous administration leads to vascular obliterating.

Ointments and gels containing venoprotectors are used topically to treat varicose veins. There are *Cyclo 3 crem, Ginkgo biloba gel, troxerutin ointment, Venitan gel,* etc. Besides, anti-inflammatory and antiallergic drugs (e. g., glucocorticoids), antibacterial drugs (local antibiotics and antiseptics), and drugs providing wounds healing (methyluracil ointment) are used. At varicose veins, anticoagulants, antiaggregants, fibrinolytics, and drugs improving rheological properties of blood (pentoxifylline, rheopolyglucin, etc.) are used to prevent thrombosis.

DRUGS INFLUENCING DIGESTIVE SYSTEM

Drugs Influencing Appetite

Appetite is an emotional feeling about human desire to eat certain foods. Appetite is realized by neurohumoral way. Nervous system has the predominant role in this regulation. Appetite is under control of hunger centre (lateral nuclei of the hypothalamus) and saturation centre (ventromedial nuclei of the hypothalamus). These centres receive impulses from the gustatory, visual, and olfactory systems. An appetite largely depends on the state of cortex and limbic system.

The primary importance in the regulation of appetite belongs to such mediators as noradrenaline, serotonin, and dopamine influecing the appropriate receptors (β_1- and β_2-adrenergic receptors, α_1-adrenergic receptors, 5-HT_{1B} and 5-HT_{2C}-serotoninergic receptors, D_1-dopaminergic receptors). Besides, specific neuropeptides regulating appetite and energetic balance are in hypothalamus. Appetite-increasing substances (orexigens) are neuropeptide Y, orexigens A and B, ghrelin (stomach peptide which after absorption in the blood stimulates growth hormone production by hypothalamus), hormone stimulating the growth hormone secretion, GABA, etc.

There are substances which reduce appetite (anorexigenic substances). They are leptin (hormone of fatty cells which penetrates into the brain and stimulates production of anorectic substances by hypothalamus and simultaneously inhibits the secretion of orexigenic substances), α-melanocyte-stimulating hormone, hormones stimulating release of thyrotropin, neurotensin, serotonin, cholecystokinin, glucagon-like compounds, etc.

Drugs Increasing Appetite

Appetite is stimulated by means of taste and extractive substances of pepper, cinnamon, cloves, bay leaf, garlic, onion, horseradish, dill, mustard, etc. Broth, vegetable broths, juices, mineral water, dry wine, and beer also have stimulating influence upon appetite.

Medicines which are used to stimulate appetite and gastric juice secretion include bitters: tinctures of wormwood, centaury ordinary, water shamrock, rhizome of calamus, etc. These drugs are taken 15–20 minutes before a meal.

Mechanism of their action is associated with stimulation of receptors in oral cavity that results in increase of reflex excitability of hunger centre. Owing to this, first (complex-reflex) phase of gastric secretion is enhanced at meal.

Drugs increasing appetite also include insulin, aminazine, amitriptyline, lithium carbonate, clonidine, and anabolic steroids.

Drugs Decreasing Appetite (Anorexic or Anorexigenic Drugs)

Drugs decreasing an appetite are called anorexigenic drugs or appetite suppressants. Anorexigenic drugs are used in the treatment for alimentary obesity. This disease is accompanied by metabolic disordes which increase the hazard of diabetes mellitus, cardiovascular diseases, etc.

The main mode of obesity treatment is to decrease amount of high energy value food and increase of physical activity.

According to mechanism of action, anorexigenic drugs are classified as follows:

1. Drugs stimulating catecholaminergic system of brain: *amphetamine, chlorphentermine (Desopimon), mazindol,* and *amfepramone (phepranone).*
2. Drugs stimulating serotoninergic system of brain: *fenfluramine, dexfenfluramine*.
3. Drug stimulating both catecholaminergic and serotoninergic systems of brain: *sibutramine*.
4. Inhibitor of gastrointestinal lipases: *orlistat*.

Active anorexigenic drug *amphetamine (phenaminum)* is a derivative of phenylalkylamine. The drug exhibits both central and peripheral adrenomimetic action. Amphtamine increases the release of norepinephrine and dopamine by nerve terminals and supresses their reuptake. It is accompanied by excitation of central adrenergic and dopaminergic receptors and reduction of hunger feeling. Owing to excitation of corresponding receptors, the drug causes a lot of side effects: insomnia, agitation, tachycardia, increased blood pressure, etc. Besides, phenaminum intake can result in both physical and psychical dependence. With reference to above mentioned, phenaminum is not used presently as anorexigenic drug.

Amfepramone (phepranone) is a derivative of phenylalkylamine. Its mechanism of action is identical to those of phenaminum. But phepranone stimulates central and peripheral nervous systems in less degree. Phepranone is taken orally 30–60 minutes before a meal. Because the drug can cause insomnia, it should be taken in the first half of a day. Its possible side effects are agitation, insomnia, tachycardia, increase of blood pressure, etc. Long-lasting phepranone intake leads to tolerance and drug dependence.

Fenfluramine selectively acts in serotoninergic synapses and inhibits neuronal reuptake of serotonin. The drug inhibits central nervous system and increases blood pressure.

Sibutramine simultaneously inhibits neuronal reuptake of norepinephrine, serotonin, and dopamine. The drug decreases blood concentration of uric acid and lipids. The following side effects are observed at sibutramine therapy: tachycardia, sleep disorders, headache, and increased excitability of central nervous system.

A decrease of intestinal lipid absorption is one of the ways of treating obesity. It is achieved by inhibition of lipase activity (enzyme which is necessary for lipid absorption). This mechanism of action is typical for *orlistat*. The drug inhibits lipase in stomach and intestine that reduces hydrolysis of dietary triglycerides. Lipid absorption is decreased by 30 %. Also, orlistat inhibits absorption of lipid-soluble vitamins. About 83 % absorbed drug dose is excreted

through intestine in unchanged form. Full elimination of orlistat occurs during 3–5 days. Side effects depend on triglycerides level in food and include urging to stool, abdominal pain, diarrhoea, nausea, and vomiting.

Restriction use of sugar or use of sweeteners (saccharin, etc.) is also recomemded for decrease of calorie food. Sweeteners have a low calorie and are badly absorbed from intestine.

Recently, hormon of fat cells *leptin* is recommended for reduction of appetite. Its administration promotes the lowering of body weight in patient with obesity. But, the drug is effective only in patients with deficiency of endogenous leptin.

Melanocortins inhibit an appetite owing to interaction with specific MC_4-receptors. Other agonists of these receptors also have anorexigenic effect.

Cholecystokinin is also noteworthy. Besides the regulation of functions of digestive system, this hormon also acts as saturation factor. Series of compounds activating the cholecystokinin system are now being studied.

It should be borne in mind that pharmacotherapy of obesity has auxiliary character and the base of obesity treatment is combination of low-calorie diet with additional physical activity.

Drugs Influencing Function of Salivary Glands

Salivary glands secretion is under control of both parasympathetic and sympathetic nervous systems. The tone of parasympathetic nervous system is predominante; therefore, stimulation of M-cholinoceptors, located in salivary glands, determines the degree of salivation.

Drugs with M-cholinomimetic activity (*proserinum*, *carbacholine*, *pilocarpine*, *aceclidine*, etc.) increase salivation. Cholinoblocking drugs (*atropine*, *scopolamine*, etc.) inhibit salivation. Drugs with blocking activity are used to reduce hypersalivation at Parkinson disease, helminth infestation, and poisoning by heavy metals.

Drugs Used in Hyposecretion of Digestive Glands

Hypofunction of digestive glands (stomach, pancreas, liver) is accompanied by malnutrition of the body and disorders of gastrointestinal motility. Wherein, disorders of function of one organ can leads to secretory disorders of other organs.

Drugs Used in Hyposecretion of Stomach

Mucosa of stomach secretes several enzymes, the main of which is pepsinogen. Its transformation to active pepsin occurs in the acidic environment. Necessary acidity is achieved owing to secretory activity of parietal cells producing hydrochloric acid (precisely, ions of hydrogen).

Hypofunction of gastric glands occurs in 10–15 % practically healthy people. Sometimes, it is only insufficient secretion of hydrochloric acid, but quite often it combines with hyposecretion of pepsinogen. Hyposecretion can cause inflammation with development of hypoacid gastritis.

Vagus nerve and several gastrointestinal hormones regulate the stomach secretion. It is known, that the increase of vagal tone and the release of gastrin and histamine result in the elevation of gastric secretion. In turn, reduction of cholinergic influence and suppression of gastrin or histamine release cause the decrease of gastric juice secretion. Endogenous substances supressing gastric secretion are secretin, cholecystokinin, prostaglandins, vasoactive intestinal peptide, peptide inhibiting gastric secretion, etc.

Administration of gastrin, histamine or extractive substances can significantly increase gastric secretion in patients with hypoacid gastritis which is caused by functional disorders. But administration of these substances does not increase secretion in patients with organic lesions of the gastric mucosa. Thereby, these substances may be used for diagnostics of gastric pathology.

Pentagastrin is a synthetic histamine analogue. The drug stimulates gastric secretion. Pharmaceutical industry produces 0.025 % ampoule solution of pentagastrin. The drug is administered subcutaneously to diagnose stomach pathology. Sampling of gastric

juice is carried out every 15 minutes after pentagastrin injection. Its administration allows to estimate the secretory ability of stomach and to determine the character of stomach damages. At functional insufficiency of gastric mucosa, pentagastrin increases the secretion. But secretion is not increased in patietns with organic diseases of the stomach.

Attempts to increase secretion have low efficiency or are completely ineffective in patients with hypoacid gastritis which is accompanied by atrophic process. Therefore, treatment of patients with such pathological states needs the drugs of substitutive therapy. With this end in view, such drugs as *natural gastric juice*, *pepsin*, *diluted hydrochloric acid*, *acidin-pepsin*, *abomin*, and *carbonated mineral water* are used.

The most physiological drug is *natural gastric juice*, which is obtained from animals. The drug is taken with meals in dose 1 tablespoon. *Artificial gastric juice* (obtained by insisting of stomach mucosa of pigs in 0.2–0.5 % hydrochloric acid solution) is less active. It is taken also with meals in dose 1–2 tablespoons.

Abomin is tableted drug obtained from gastric mucosa of calves and lambs. It is taken with meals in dose 1–2 tablets. Course of treatment is 1–3 months. Abomin contains several proteolytic gastric enzymes. The treatment with this drug needs simultaneous intake of hydrochloric acid.

Pepsin is obtained from gastric mucosa of pigs. Mixture of pepsin and hydrochloric acid is used with meals in dose 1 tablespoon.

Acidin-pepsin is used in patients with hypoacid gastritis. One tablet of drug is dissolved in 1/2 glass of water and is taken during or immediately after eating.

Hydrochloric acid is used to treat hypoacid gastritis without pepsin deficiency. Diluted standard solution of hydrochloric acid is taken with meals in dose 10–15 drops with 1/2 glass of water. This solution in recommended to take through tubule to prevent tooth enamel destruction. Organic acids (malic, citric, or acetic) are also used in hypoacid gastritis. These acids realease hydrogen ions in stomach and undergo absorption and energy metabolism in body.

An eating of acidic foods, such as sauerkraut, fruits, etc. also is recommended.

Drugs Used in Hypersecretion of Gastric Glands and in Disorders of Trophism and Regeneration of Gastric Mucosa

These drugs are used in patients with hyperacid gastritis, ulcer disease of stomach and duodenum. According to studies, approximately 10 % of 30–55-year-old males and 6 % of females under 55 years suffer from ulcer disease. Ulcer disease lasts for years and is characterized by periods of exacerbation and remission.

According to modern ideas, ulcer disease is a result of imbalance between protective and agressive factors influecing upon the stomach mucus.

Acid-peptide (predominant role of hydrochloric acid) influence and *Helicobacter pylori* have leading part between aggressive factors. Other agressive factors are bile components, certain drugs (e. g., nonsteroidal anti-inflammatory agents and glucocorticoids), thermal and mechanical lesions of the mucous membrane, frequent stressful situations, etc.

Protective factors include mucosal barrier, microcirculation, regenerative ability of mucous membrane of stomach and duodenum, bicarbonate secretion, etc.

Considering the above-mentioned factors, the main aims of ulcer disease therapy are:

– decrease of acid-peptide aggression;

– antibacterial therapy against *Helicobacter pylori*;

– increase of protective ability of mucous membrane of stomach and duodenum;

– stimulation of regeneration on the ulcer surface.

Drugs Decreasing Secretory Activity of Gastric Glands

This group occupies the central position in treatment of ulcer disease of stomach and duodenum, hyperacid gastritis, esophagitis, and Zollinger-Ellison syndrome. To understand the mechanisms of drugs action, it is necessary to consider the mechanisms of secretion regulation at the cellular level.

Secretion of gastric juice occurs continuously throughout the day (nearly 2–3 *l* a day) and sharply increases during digestion. Mucous membrane of stomach contains 3 types of cells: chief cells secreting pepsinogen, parietal cells secreting hydrogen ions, and surface mucous cells (foveolar cells) secreting mucin and bicarbonate. M_3-cholinergic, H_2-histaminergic, and gastrinergic receptors are located in parietal cell membranes. Stimulation of these receptors leads to an increase of proton pump activity. In turn, proton pump secretes hydrogen ions in the stomach cavity. An increase of gastric juice acidity promotes transformation of pepsinogen to pepsin. Also, acetylcholine, gastrin, and histamine increase the secretion of pepsinogen by chief cells. M-cholinolytics, H_2-histamine receptor antagonists, and proton pump inhibitors are used to decrease parietal cell secretion. Especially pronounced therapeutic effect of these drugs is observed in patients with ulcer disease of duodenum, in which acid-peptic factor is greater.

Drugs decreasing the gastric secretion are classified as follows.

1. M-cholinoceptor antagonists:

– nonselective M-cholinergic antagonists: *atropine*, *platyphyllin*, and *metacinium*;

– drugs blocking predominantly M_1-cholinoceptors: *pirenzepine* and *telenzepine*.

2. H_2-histaminergic receptor antagonists: *cimetidine*, *ranitidine*, *famotidine*, *nizatidine*, and *roxatidine*.

3. Proton pump inhibitors: *omeprazole*, *pantoprazole*, *lansoprazole*, *rabeprazole*, and *esomeprazole*.

4. Prostaglandins and their synthetic analogues: *misoprostol*.

5. Gastrin receptor antagonists: *proglumide*.

M-Cholinoceptor Antagonists

This group includes *atropine, platyphyllin, metacinium, pirenzepine (Gastrozepin),* and *telenzepine*. Depending on their affinity to the different types of M-cholinoceptors, these drugs are devided into selective (blocking only M_1-cholinoceptors) and nonselective (blocking all types of M-cholinoceptors) M-cholinergic antagonists. Nonselective drugs (*atropine, platyphyllin, metacinium*) are the first agents which were used to treat ulcer disease and hyperacid gastritis. Mechanism of their action is associated with blockage of M_3-cholinergic receptors which are located in membranes of the cells of mucous membrane of stomach and in the cells of smooth muscles of gastrointestinal tract. Drugs eliminate vagal influence predominantly upon basal and nocturnal secretion. These drugs exert less influence upon stimulated secretion. These drugs decrease gastric juice volume as well as hydrochloric acid concentration in it. Simultaneously, nonselective M-cholinoblockers reduce the tone of stomach and intestine and prolong gastric emptying time that leads to activation of gastric secretion owing to gastric distension.

It should be noticed that clinically significant antisecretory effect of M-cholinergic antagonists develops in case of high degree of blockage of M-cholinergic receptors. As a rule, such degree of blockage is accompanied by lot of side effects (constipation, dry mouth, accommodation disorders, tachycardia, etc.). Therapeutic effect of M-cholinergic antagonists quickly reduces owing to tolerance.

Practically, such nonselective drugs are used as *tincture* and *extract* of *Belladonna*; tablets and injections of *atropine, platyphyllin, metacinium*, etc. Co-formulated drugs are used: "*Bekarbon*", "*Bellastezin*", "*Bellalgin*", etc. Nonselective drugs are used to reduce hypertonus of pyloric section with delayed food evacuation and to relieve cramping (spasmodic pains).

Pirenzepine and *telenzepine*, selective M_1-cholinergic antagonists, are mainly used presently. These drugs exhibit high affinity to M_1-cholinergic receptors of parasympathetic ganglia of

stomach. It results in low probability of side effects. Besides, there is evidence that these drugs increase the mucosal resistance to damaging factors.

Pirenzepine is administered parenterally and taken orally. Its gastrointestinal bioavailability is 20–30 %. Maximal concentration in blood is achived in 2 hours after drug intake. Absorbed pirenzepine binds with plasma proteins in insignificant degree. The drug is excreted predominantly with bile in unmodified form. Pirenzepine is prescribed 2 times a day for 15–20 minutes prior a meal. Therapeutic course lasts 3–4 weeks. Long-time intake of high doses of pirenzepine can cause side effects which is typical for nonselective M-cholinergic antagonists: dry mouth, tachycardia, etc.

Telenzepine is 25 times more active M_1-cholinergic antagonist than pirenzepine. Besides marked inhibition of gastric secretion, the drug significantly suppresses secretion of salivary glands that restricts its clinical use.

H_2-Histaminergic Antagonists

H_2-histaminergic antagonists are classified as follows:

– I-generation drug: *cimetidine*;

– II–generation drug: *ranitidine* (*Zantac*);

– III-generation drug: *famotidine* (*Quamatel*);

– IV-generation drug: *nizatidine* (*Axid*);

– V-generation drug: *roxatidine* (*Roxane*).

This classification is based on different pharmacological activity of the drugs and differences in their pharmacokinetics and side effects.

H_2-histaminergic antagonists block corresponding receptors at competitive type. The drugs of II–V generations exert significantly higher degree of affinity to H_2-receptors. Therefore, it is possible to prescribe these drugs in significantly less doses. H_2-histaminergic antagonists inhibit basal and nocturnal secretion, as well as secretion stimulated by food, gastric distension, histamine, etc. Drugs increase the production of prostaglandin E_2 by the mucosal membrane of

stomach and duodenum. It results in gastroprotective effect, owing to which drugs promote the ulcer healing.

It should be noticed that sharp discontinuation of drug intake (except nizatidine and roxatidine) can result in rebound syndrome. This phenomenon is caused by hypergastrinemia which is developed owing to decrease of gastric juice acidity and increase of density of H_2-histaminergic receptors and its affinity to histamine. Therefore, discontinuation of therapy with these drugs should be gradual with simultaneous use of other antisecretory agents.

H_2-histaminergic antagonists are administered intravenously and taken orally. Their gastrointestinal bioavailability varies from 50 to 90 %. Degree of binding with plasma proteins is 15–20 %. Drugs easily penetrate placenta and may be secreted with breast milk. Cimetidine easily penetrates through blood-brain barrier. Duration of cimetidine effect is 6 hours, ranitidine – 8–12 hours, famotidine – 12–24 hours, nizatidine and roxatidine – more than 24 hours. Ranitidine is prescribed 2 times a day (at the morning 30 minutes before a meal and at night), famotidine and other drugs – once a day at night. Course of treatment lasts from 4 to 6 weeks.

Cimetidine is low-active, short-acting, and rather toxic drug. It blocks androgenic receptors that leads to gynecomasty and sexual disorders in males; inhibits microsomal hepatic enzymes, therefore, potentiates effects of some medicines (e. g., diazepam, propranolol, theophylline). Long-time use of cimetidine can provoke leukopenia. Therefore, cimetidine is not used in medicine nowadays.

Less than 50 % dose of ranitidine is metabolized in the body. Famotidine and other drugs are not metabolized practically. The main route of their excretion is kidneys.

Mechanism of action of *ranitidine bismuth citrate* (*Pylorid*) is associated with blockage of H_2-histaminergic receptors. Besides, the drug exerts high bactericidal activity against *Helicobacter pylori.*

Indications for clinical use of H_2-histamenergic antagonists are the following:

– ulcer disease of stomach and duodenum;

– hyperacid gastritis;

– duodenitis, esophagitis, and other diseases which are accompanied by increasing secretion of hydrochloric acid;

– prevention of ulcers and erosions in patients with craniocerebral traumas, sepsis significant burns, etc;

– emergency in bleeding ulcers of stomach, duodenum, and esophagus (0.05 g ranitidine is administered intravenously every 6–8 hours).

Side effects of H_2-histaminergic drugs are diarrhoea, constipation, skin rash, headache, myalgia, and dizziness.

Due to binding with H_2-histaminergic receptors of blood cells, drugs can provoke leukopenia, thrombocytopenia, and haemolytic anaemia. Blockage of H_2-histaminergic receptors in the membranes of tissue basophils cal cause the aggravation of bronchial asthma, cutaneous manifestations of systemic lupus erythematosus, etc.

It should be noticed that long-lasting artificial inhibition of gastric acidity promotes cancerogenesis.

Proton Pump Inhibitors

Proton pump inhibitors include *omeprazole, pantoprazole, lansoprazole, rabeprazole,* etc.

Single way of hydrochloric acid secretion exists independently on mode of stimulation (acetylcholine, histamine, gastrin, etc.). It is reliased on the level of membranes of parietal cells by means of energy-dependent exchange of potassium ions and hydrogen ions. There is specific H^+, K^+-ATPase in parietal cell membranes which provides secretion of hydrogen ions into stomach cavity and entry of potassium ions into the blood.

Based on these data, drugs blocking H^+, K^+-ATPase activity were established. All proton pump inhibitors are prodrugs. In acidic environment near parietal cells, these drugs are transformed to active metabolites – sulfenamides, which interact with sulfhydryl groups of H^+, K^+-ATPase. Proton pump inhibitors markedly decrease basal, nocturnal, and stimulated secretion of hydrochloric acid. These drugs are also effective in cases which are resistive to M-cholinergic and

H_2-histaminergic antagonists. It should be noticed that these drugs also suppress the activity of H^+, K^+-ATPase of *Helicobacter pylori* that results in bacteriostatic effect.

Therapy with proton pump inhibitors is accompanied by an increase of gastrin concentration in the blood. Therefore, sudden discontinuation of the drug intake can cause the rebound syndrome. In this regard, cessation of proton pump inhibitor intake should be under the shelter of antacids.

Proton pump inhibitors are administered intravenously or taken orally before a breakfast. Drugs are poorly absorbed in acidic enviroment; therefore, proton pump inhibitors should be taken together with sodium hydrocarbonate solurion. Enteric-soluble granules of drugs are protected by means of gelatin capsules from hydrochloric acid. Therefore, it is impossible to chew them. Their gastrointestinal bioavailability is 35–50 %. The degree of binding with plasma proteins is about 95 %. Proton pump inhibitors undergo the hepatic biotransformation. Maximum effect develops in 1–2 hours after drugs intake. Proton pump inhibitors are accumulated in acidic environment of parietal cells where they exert their effect. Proton pump inhibitors are taken once a day. Their effect persists for 24 hours (sometimes up to 3–4 days). Such long-lasting effect is due to irreversible inhibition of proton pump. Thereby, a new synthesized enzyme is needed for restoration of secretion. It should be noticed that about 1/2 of human H^+, K^+-ATPase is restored during 30–48 hours.

Indications for clinical use of proton pump inhibitors are identical with indications of H_2-histaminergic antagonists.

The following side effects are observed during treatment with proton pump inhibitors: headache, drowsiness, dizziness, diarrhoea or constipation, and abdominal pain. These phenomena arise after first drug intake and, as a rule, disappear in 1–2 days. Visual and hearing disorders are described in case of intravenous drug administration. Long-time administration of proton pump inhibitors is accompanied by risk of mucous membrane hyperplasia with formation of carcinoids in submucosal layer of stomach.

Prostaglandins and Their Synthetic Analogues

Representative of this group is *misoprostol* (synthetic analogue of prostaglandin E_1). The drug exhibits two dose-dependent effects. Low doses of the drug exert gastroprotective effect owing to the increase of secretion of bicarbonates and mucus and microcirculation improving. Large doses of the drug cause blockage of hydrochloric acid secretion. Misoprostol blocks both basal and stimulated secretion of hydrochloric acid. Misoprostol is used to treat erosions and ulcer disease of stomach and duodenum. The drug is taken in tablets 3–4 times a day (with meals and at night). Course of treatment lasts 3–8 weeks. Side effects of misoprostol are abdominal pain, meteorism, diarrhoea, allergic reactions, decrease of blood pressure, etc.

Gastrin Receptor Antagonists

Representative of this group is *proglumide*. The drug inhibits gastrointestinal motility and reduces gastric secretion. Its mechanism of action is associated with blockage of both CCK_A and CCK_B subtypes of gastrin receptors. Antisecretory activity of proglumide is equivalent to the first generation of H_2-histaminergic antagonists.

Gastroprotective Drugs

This group includes drugs with different chemical structure and mechanisms of action, which provide protection of gastric mucosa from aggressive influence and/or create conditions for ulcers healing or stimulate this process. Basically, gastroprotectors are used to treat ulcer disease of stomach and duodenum.

Gastroprotectors are classified as follows:

1) drugs creating mechanical protection of gastric mucosa: *sucralfate (Venter), bismuth subcitrate (De-nol).*

2) drugs increasing protective function of mucous barrier: *carbenoxolone, misoprostol.*

Sucralfate (*Venter*) is sulfated disaccharide in complex with aluminum hydroxide. Sucralfate is polymerized in acid enviroment

of stomach. Polymerized molecules exert significant negative charge, owing to which drug binds with positively charged protein radicals of the damaged surface. The sucralfate concentration on the ulcer surface is 5–7 times more than on the healthy mucosa. Protective pellicle is held on the ulcer surface of stomach up to 8 hours and on the duodenal ulcer – up to 4 hours. Sucralfate is taken 4 times a day: 3 times in 30 minutes prior a meal and once at night. Duration of treatment is 4–6 weeks.

Sucralfate does not decrease secretion of hydrochloric acid and pepsin, but these substances can be absorbed on the surface of drug molecules.

Sucralfate is well tolerated by patients. Its intake can result in the following side effects: epigastric discomfort, dry mouth, itching and redness of the skin. Sucralfate is able to decrease intestinal absorption of phosphate and fluoride. The drug is contraindicated in pregnant women, children up to 4 years of age, and nursing mothers.

De-nol is colloidal bismuth subcitrate, which forms complex with proteins in acidic environment. Most of the drug is concentrated in erosive surface and protect it from damage. Besides, the gastroprotective activity of De-nol relates to its ability to increase the local synthesis of prostaglandin E_2 by mucosa of gastric antrum and duodenum. Due to this, De-nol improves the microcirculation and stimulates the secretion of hydrocarbonate. The drug exerts bactericidal effect against *Helicobacter pylori*. Bacteria disappear from the mucosal surface in 30–90 minutes after De-nol intake. Pathogen is not completely detected after 3 weeks of treatment, but discontinuation of De-nol intake can be accompanied by recolonization of *Helicobacter pylori*. Therefore, combination of De-nol with antibacterial drugs is most appropriate.

De-nol is taken in 30 minutes before a meal and at night. Course of treatment lasts 4–6 weeks.

The drug is well tolerated by patients. Its side effects are nausea, vomiting, diarrhoea, headache, and dizziness. Bismuth sulfide (formed in the intestines) stains tongue and feces black.

Carbenoxolone (Biogastron) is glycyrrhizic acid of licorice root. The drug stimulates mucus secretion and increases its viscosity. Besides, carbenoxolone inhibits enzymes participating in prostaglandin inactivation. Carbenoxolone exerts some mineralocorticoid and anti-inflammatory activity. The drug inhibits the transformation of pepsinogen to pepsin.

Orally taken carbenoxolone is absorbed from the stomach. The degree of binding with plasma proteins is 80–90 %. Carbenoxolone is excreted from the body by kidneys (60 %) and partly – by liver. It should be noted, that drug undergoes enterohepatic recycling.

Carbenoxolone is taken 30 minutes before a meal and at night. The drug is mainly used to treat ulcer disease in patient with high secretory rate. Sometimes, the drug is used to treat duodenal ulcers.

Side effects of carbenoxolone are the result of its mineralocorticoid activity and include oedemas, body weight gain, hypertension, muscular weakness, etc.

Misoprostol is a synthetic analogue of prostaglandin E_1. It is known that gastric mucosa synthesizes prostaglandins, which stimulate secretion of mucus and bicarbonate, inhibit secretion of hydrogen ions by parietal cells, expand the vessels of deep layers of mucosa, increase the resistance of vascular wall to aggressive factors, and promote healing of erosions and ulcers.

Especially pronounced gastroprotective effect of misoprostol is observed at treatment of ulcers, which are developed owing to the use of steroidal and nonsteroidal anti-inflammatory drugs (these drugs inhibit prostaglandin synthesis). Misoprostol is taken with meals 3–4 times a day. Its effect develops in 30 minutes and lasts up to 3 hours. Duration of treatment is 4–8 weeks. Misoprostol is not used as drug for monotherapy due to frequent side effects which include abdominal pain, nausea, vomiting, rash, uterine bleeding during menstruation, etc. Drug is predominantly recommended to prevent ulcers in patient treated by anti-inflammatory drugs.

Somatostatin is also can be referred as gastroprotector. This drug is used to interrupt bleeding from peptic ulcer.

Antacids

This group includes the following drugs: *sodium hydrocarbonate, calcium carbonate, magnesium oxide, aluminium hydroxide, Almagel, Phosphalugel, Maalox, Gastal*, etc.

These drugs are weak bases which inactivate hydrochloric acid by means of direct chemical interaction with it.

Depending on their ability to be absorbed from gastrointestinal tract, antacids are divided into drugs of resorptive action and drugs of pre-resorptive action. Drugs of resorptive action are *sodium hydrocarbonate* and *calcium carbonate*.

Sodium hydrocarbonate is highly soluble in water. After intake, drug is readily distributed in stomach. The drug exerts almost lightning, but short antacid effect. Duration of its effect is 15–20 minutes. Interaction of sodium hydrocarbonate with hydrochloric acid is accompanied by carbon dioxide release which expands the stomach. It results in belching gas and the feeling of heaviness in epigastrium. Rebound syndrome is typical for sodium hydrocarbonate, because gastric distension leads to secondary increase of secretion of hydrochloric acid and pepsin that is the cause of fast resumption of pain.

Long-time intake of sodium hydrocarbonate can result in the systemic alkalosis owing to absorption of bicarbonate ions. A risk of this complication increases in patients with impaired renal function. Symptoms of systemic alkalosis include poor appetite, nausea, vomiting, weakness, abdominal pain, muscular spasms, and convulsions. Also, long-lasting intake of sodium hydrocarbonate is accompanied by accumulation of sodium ions, increased blood pressure, and oedemas.

Calcium carbonate is poorly soluble in gastric contents. Its action is slow, and absorption is less than absorption of sodium hydrocaronate. Drug neutralizes hydrochloric acid with the release of carbon dioxide. Calcium carbonate causes most pronounced rebound syndrome. Regular drug intake together with milk diet (typical diet for patients with ulcer disease) is accompanied by calcium retention

in the body and development of “milk alkali syndrome”. Symptoms of this syndrome include nausea, vomiting, polyuria, hypercalcemia, calcification of vessels and kidneys, formation of renal stones, azotemia, and psychical disorders.

Pre-resorptive antacids are magnesium oxide, aluminium hydroxide, Almagel and other drugs.

Magnesium oxide interacts with hydrochloric acid without carbon dioxide release. Therefore, rebound syndrome is uncharacteristic of magnesium oxide intake. Magnesium chloride, synthesized in reaction of neutralization, is poorly absorbed from intestine and exerts weak laxative effect. Its laxative effect is associated with increased osmotic pressure into the intestine and stimulation of secretion of cholecystokinin that stimulates peristalsis. Magnesium oxide does not influence systemic acid-base balance. Its antacid effect develops slowly.

Aluminium hydroxide exerts both antacid and absorptive effects. The drug interacts with hydrochloric acid without carbon dioxide release. Systemic alkalosis is uncharacteristic of regular intake of aluminium hyroxide. But, regular drug intake can lead to slowdown of intestinal motility that promotes constipation. A part of administered dose, which does not interact with hydrochloric acid, turns into phosphate and carbonate. These aluminium salts is poorly absorbable in the intestine. Therefore, regular aluminium hydroxide intake reduces absorption of phosphates and can cause hypophosphatemia and hypophosphaturia. Deficiency of phosphates is manifested by fatigability, muscular weakness, thinking disturbances, anorexia, etc. Prolonged phosphate deficiency is accompanied by bone lesions (osteoporosis, osteomalacia), impaired healing of wound, and increased risk of infections. Besides, aluminium binds fluoride ions into intestine that results in damage to dental enamel.

Co-formulated antacid drugs are widely used in medicine to decrease risk of side effects and to increase drug efficacy. These drugs include *Almagel, Posphalugel, Maalox, Gastal*, etc.

Almagel consists of aluminium hydroxide gel, magnesium oxide, and sorbitol. Magnesium oxide exerts laxative effect and sorbitol – cholagogic effect. Gel-like form promotes uniform drug distribution over the gastric surface.

Almagel A contains additionally anaesthesine which causes local anaesthesia and inhibits gastrin secretion.

Phosphalugel contains aluminium phosphate in form of hydrophilic colloidal micelles, pectin gel, and agar-agar. The drug exerts antacid and absorptive effects. Micelles of aluminium hydroxide bind bacteria, viruses, toxines, and gases and eliminate them from intestine. Drug does not influence upon systemic acid-base balance and phosphate absorption. Pectin and agar-agar promote the formation of mucoid protective layer in gastrointestinal tract.

As a rule, all antacids are prescribed in 1 hour after a meal (in connection with decrease of buffering effect of food in period of maximal secretion) or in 3 hours after a meal (for restoration of antacid action after food evacuation). Also, antacids are taken before bedtime to protect mucous membrane during nocturnal secretion. In acute period of disease, the course of treatment with antacids lasts 2–4 weeks. In cases when pain arises during a meal, antacids are prescribed in 30–40 minutes before the meal.

Antacids are used to treat ulcer disease of stomach and duodenum with hyperacid syndrome, hyperacid gastritis, hiatal hernia, esophagitis, and reflux esophagitis.

Drugs Used to Treat Hypofunction of Pancreas

During a day, pancreas produces 1.5–2 *l* of juice containing more than 10 enzymes. Pancreatic juice also contains significant amount of bicarbonate and, therefore, has alkaline reaction. It promotes neutralization of hydrochloric acid and the normal activity of pancreatic enzymes involving in the digestion of peptides, lipids, and carbohydrates.

Trypsin, chymotrypsin, carboxypeptidases A and B, and elastase complete proteolysis of proteins which are initiated by pepsin.

Amylase provides the hydrolysis of polysaccharides. Lipase and phospholipase hydrolyze fatty acids and phospholipids. Bile is also necessary for hydrolysis of lipids because it promotes their emulsification. Besides, bile participates in absorption of amino acids.

Pancreatic insufficiency develops due to past acute and chronic pancreatitis and in patients suffering from chronic gastritis, ulcer disease, cholangitis, etc.

Drugs of pancreatic enzymes often contain also pepsin or bile components. Such combination increases functional integration of digestive system and is the most effective in patients with chronic digestive disordes and in elderly and senile age patients. Pancreatic enzymes are obtained from pancreas of butcher livestock, some enzymes – from microorganisms and, even, plants.

Pancreatin (powder of the dry pancreas of butcher livestock) contains predominantly two enzymes – trypsin and amylase. It is used in patients with pancreatic insufficiency. Pancreatic insufficiency is commonly laced with insufficiency of digestive function of stomach and intestine. Therefore, co-formulated drugs are commonly used in medicine: *Mezym Forte* (pancreatin contaning amylase, lipase, and protease), *Panzinorm* (drug contains pancreatin, extract of gastric mucosa, bile ecstract, amino acids), *Digestal* (consists of pancreatin, bile extract, hemicellulose), *Festal*, *Enzystal*, *Licrease*, *Kreon*, etc. All drugs act in alkaline environment and are inactivated in acidic. Therefore, drugs are manufactured in intestinal-soluble dragee or capsules. Course of treatment with pancreatic enzymes lasts from 2 up to 4–6 weeks. Regular drug intake decreases bloating and diarrhoea and improves performance status of the patient.

Drugs of pancreatic enzymes are used to treat chronic pancreatitis, achylia, chronic hypoacid gastritis, hepatitis, cholecystitis, etc.

These drugs are well tolerated by patients. It should be noticed that these drugs contain significant amounts of purines and can cause exacerbation of gout and formation of urate kidney stones.

Drugs Inhibiting Pancreatic Secretion

Drugs inhibiting pancreatic secretion are used to treat acute pancreatitis.

Normally, inactive trypsinogen is synthesized in pancreas. In duodenum, it is activated to trypsin by means of enterokinase. At acute pancreatitis, trypsinogen is converted to trypsin directly within pancreas owing to action of enteropeptidase (enterokinase). In turn, trypsin activates other proteolytic enzymes of pancreas. These processes result in autolysis and necrosis of pancreas. Simultaneously sinthesized bradykinin causes vasodilation and hypotension.

An aim of acute pancreatitis treatment is to suppress both secretion and activation of proteolytic enzymes – trypsin and kallikrein. The following drugs are used for this aim:

1. M-cholinoceptor antagonists: *atropine*, etc.;
2. Inhibitors of proteolytic enzymes: *aprotinin (Contrycal, Trasylol, Gordox), aminocaproic acid*, etc.

Contrycal is used most commonly. The drug is obtained from pulmonary tissues of livestock for slaughter. Contrycal inhibits the proteolytic enzymes and prevents or reduces the autolysis and necrosis of pancreas. Contrycal is dosed with international units (IU) and administered intravenously drop by drop.

Treatment of acute pancreatitis also includes administration of analgesics, antibiotics, antacids, plasma expanders, electrolytes, and other drugs.

Drugs Improving Hepatic Functions (Hepatotropic Drugs)

Hepatotropic drugs are devided into bile-expelling drugs, hepatoprotectors, and drugs for dissolution of gallstones.

Hepatocytes produce bile continuously. In periods between digestion, bile is deposited in large bile-ducts and in gallbladder, in which bile is concentrated. Sphincters are located in choledochous duct, gallbladder, and in major duodenal papilla (sphincter of Oddi).

Parasympathetic nervous system plays an important role in the process of bile evacuation. Increase of its tone is accompanied by relaxation of sphincters and gallbladder contraction.

Massive bile ejection occurs during digestion. It is stimulated by cholecystokinin, which is synthesized by duodenal epithelium owing to food intake. Daily volume of produced bile is about 1 L.

Process of digestion requires the bile acids which emulsify fats and activate lipase. Bile acids also promote absorption of fat-soluble vitamins (A, D, E, K, F). Besides, bile increases activity of pancreatic proteases and amylase, exerts bacteriostatic action against putrefactive intestinal microflora.

Bile-expelling drugs are devided into two groups:

1) drugs stimulating bile production (choleretics, or cholesecretics);

2) drugs promoting bile excretion (cholekinetics).

Drugs Stimulating Bile Secretion

These drugs are classified as follows.

1. Drugs containing bile and bile acids: *Allochol, Cholenzymum, liobilum, chenodeoxycholic acid*. After absorption, these drugs stimulate bile formation in hepatocytes and simultaneously exhibit function of substitutive therapy.

2. Drugs of plant origin: *Cholaflux, Cholagol, Flaminum, berberine sulfate, Cholosas, syrup of wild rose, decoctions from flowers of Helichrysum arenarium, oats seeds, Stigmatum maydis*.

3. Synthetic drugs: *oxaphenamidum, cycvalonum, nikodinum, Odeston*.

Bile-contaning drugs stimulate bile formation in hepatocytes and simultaneously perform the function of drugs for substitutive therapy.

Tablets "*Allochol*" consists of bile, garlic and nettle extracts, and activated carbon. Drug is taken orally 3 times a day after a meal. Dose is 1–2 tablets. Course of treatment is 3–4 weeks.

Tablets "*Cholenzymum*" consist of dry bile, chopped dried pancreas, and dried mucous membrane of the small intestines of slaughter cattle. Drug is taken orally, in dose 1 tablet three times a day after a meal.

Liobilum is manufactured in tablets containing 0,2 g of freeze-dried bovine bile. Drug is taken orally, in dose 1–3 tablets at the end of a meal 3 times a day. The course of treatment is 1–2 months.

Drugs of plant origin are widely used in the form of infusions, decoctions, and extracts. Cholesecretory activity is typical for flavonoids and essential oils of everlasting flower, corn silk, barberry, dandelion root, fruits of mountain ash and wild rose, etc. Pharmaceutical industry produces extracts of these plants in different medicinal forms: drops for oral intake "*Cholagol*", tablets "*Flaminum*", tablets of *berberine sulfate*, sirup "*Cholosas*".

"*Cholagol*" consists of pigments of turmeric root, frangula emodin, magnesium salicylate, peppermint oil, and eucalyptus oil. Drug has choleretic, moderate antispasmodic, anti-inflammatory, disinfectant, and laxative effects. "Cholagol" is taken 30 minutes prior a meal in dose 5–10 drops on a piece of sugar 3 times a day.

"*Flaminum*" contains dry extract Helichrysum arenarium. Drug is taken in dose 1 tablet 3 times a day 20 minutes before a meal (tablet is dissolved in 1/2 cup warm water).

Sirup "*Cholosas*" contains extractum of wild rose. "Cholosas" has choleretic and hepatoprotective effects. Drug restores and maintains normal function of hepatocytes, restore the flow of bile, normalizes the immune system. Besides, "Cholosas" has anti-inflammatory and diuretic effects, increases intestinal motility. Due to content of vitamin C and other bioactive natural products, drug improves immunity. "Cholosas" is taken 30 minutes prior a meal in dose 1 teaspoon 2–3 times a day.

Synthetic drugs (*oxaphenamidum*, *cycvalonum*, *nikodinum*, *Odeston*) increase bile production and promote its excretion. These drugs exert more prominent choleretic effect than bile-containing drugs and drugs of plant origin.

Synthetic drugs (except nikodinum) increase the tone of gallbladder and relax the smooth muscles of bile ducts. Besides, some of them (for example, nikodinum) have antimicrobial effect that is clinicaly useful in treatment of inflammatory diseases of liver, bile ducts, and gallbladder. These drugs are taken prior a meal 3 times a day.

Drugs Stimulating Bile Discharge

Cholokinetics causes the contraction of gallbladder and relaxation of Oddi sphincter that leads to bile release into the duodenum. Mechanism of action of most of them is due to irritation of duodenal mucosa owing to that cholecystokinin is released into the blood. Cholecystokinin itself causes the release of bile.

Cholecystokinin is a duodenal hormone, molecules of which consist of 33 residues of aminoacids. The drug is obtained from duodenal mucosa of pigs. Cholecystokinin promotes the gallbladder contraction, activates pancreatic secretion, and inhibits hydrochloric acid secretion by parietal cells of stomach. Cholecystokinin is used for diagnostics of gallbladder contractility and its content.

Magnesium sulfate is administered in a warm solution (25–10 % of 50–200 ml respectively) by means of duodenal probe one time in several days or taken orally (25 % solution in dose 1 tablespoon) 3–4 times a day during 2–3 weeks. The drug also may be used for tubage. In this case, patient, lying on his right side, drinks for 30 minutes 100 ml of 10–20 % magnesium sulfate solution. After this, patient should lie during 1.5–2 hours with hotty over the liver area.

Also, the following drugs are used as cholokinetics: *sorbitol* (50–70 ml of 10 % solution, 2–3 times a day before meals), *sunflower* or *olive oil* (1–2 tablespoons 2–3 times a day, it is possible to mix with lemon juice), plants containing bitters (*dandelion, yarrow, wormwood*, etc.), *essential oils of coriander* and *cumin, extracts* and *fruit juice of cranberries, cowberry,* etc.

Cholokinetics are used in the treatment for dyskinesia, chronic hepatitis, hypoacidic and anacidic gastritis. Drugs are contraindicated

in acute period of hepatic diseases, at cholelithiasis, at exacerbation of hyperacid gastritis and ulcer disease.

Myotropic antispasmodics *(No-spa, papaverine, Nicoverin, atropine, platyphyllin),* are used to reduce spasticity of bile ducts. These drugs reduce pain occurred in pathology of bile ducts. Myotropic spasmolytics are effective in moderate pain and well combined with other hepatotropic drugs. At intensive pain due to cholelithiasis attack, these drugs are administered parenterally together with analgesics.

Hepatoprotectors

As hepatoprotectors are reffered drugs increasing the resistance of liver to unfavourable factors and decreasing the damage and destruction of hepatocytes.

Hepatoprotective effect is due to the normalization of hepatocyte metabolism, the increase of microsomal enzymes activity, and restoration of damaged cell membranes. Drugs are used to treat acute and chronic hepatitis, hepatic dystrophy, cirrhosis, and toxic liver damages (including alcoholism and hepatic coma).

Hepatoprotectors obtained from thistle (*Silybum marianum*) and other plants richest on flavonoids are used most widely in medicine: *Legalon, Carsil, Siliborum, Silibinin, Rosanol, Catergen, Hepabene, Hepatofalk Planta, LIV-52,* etc.

Flavonoids are phenolic compounds – derivative of chromone. Together with ascorbic acid, flavonoids participate in redox processes and are the part of cellular antioxidant system. Flavonoids exert anti-inflammatory, bile-expelling, antiviral, analgesic, and immunomodulatory effects. These agents stabilize the vascular wall, improve the hemophoresis, reduce vascular spasm, increase level of calcium and glucocorticoids in the blood, and decrease cholesterol level. Flavonoids are widely used to prevent gastric, hepatic, and cardiovascular diseases. Their antioxidative activity is higher than activity of vitamin E. Flavonoids are easily absorbed in gastrointestinal tract and accumulated in the liver and kidneys.

Flavonoids of *Silybum marianum* exert high hepatotropism so that these drugs are highly effective at hepatic diseases. Besides, these drugs stimulate protein synthesis, normalize phospholipids metabolism, and increase the glutathione reserve in a liver.

Legalon is an extract of *Silybum marianum* fruits. The drug contains mixture of flavonoids with hepatoprotective activity – silibinin, silimarin, etc. Mechanism of Legalon action is associated with stabilization of hepatocyte membranes and antioxidative properties. The drug stimulates protein synthesis, normalizes phospholipids metabolism, and increases the glutathione reserve in the liver. Legalon is taken orally in capsules, dragee, and emulsion. The drug is low toxic and well tolerated by patients.

Presently, monopreparation of flavonoid silibinin is approved in medicine – *silibinin dihydrosuccinate sodium (Legalon SIL)*. The drug is administered intravenously to treat poisoning by death cup (*Amanita phalloides*).

Another group of hepatoprotectors is presented by drugs which are involved in the building of cellular membranes (unsaturated fatty acids, choline, phospholipids, essential amino acids, etc). As a rule, these drugs also contain vitamins which participate in detoxifying function of liver and in restoration of cellular membranes. This group includes such drugs as *Essentiale, thiotriazoline, ademetionine, lipoic (thioctic) acid,* etc.

Essentiale contains unsaturated fatty acids as part of phospholipids, vitamins of group B, and tocopherol. The drug is administered intravenously in crucial cases (hepatic coma, acute poisoning with hepatic dysfunction, etc.). Also, Essentiale is taken orally to treat chronic hepatitis, liver cirrhosis, hepatic dysfunction in patients with diabetes mellitus, to prevent cholelithiasis reccurence, in pre- and postoperative periods, etc. Dose for oral intake is 2–3 capsules 3 times a day before a meal.

Thiotriazoline is synthetic agent with anti-ischaemic, antioxidative, membrane stabilizing, and immunomodulatory activity. Drug prevents hepatocytes destruction, inhibits fatty infiltration and necrosis of liver. Thiotriazoline normalizes peptide,

carbohydrate, and pigmentary metabolism in the liver. Thiotriazoline stimulates both synthesis and discharge of bile. Besides, thiotriazoline reduces the ischemia of myocardium, decreases the necrotic zones after myocardial infarction, and activates fibrinolytic properties of blood. Drug is administered intravenously and intramuscularly in hepatitis, hepatic cirrhosis, ischaemic heart disease, myocardial infarction, cardiosclerosis, and arrhythmias.

Ademetionine (*Heptral*) contains the methyl groups which are essential to synthesis of membrane phospholipids, cysteine, glutathione, and taurine. These substances are essential for detoxifying function of liver. Besides, ademetionine exerts antidepressive, analgesic, and anti-inflammatory effects. The drug is taken orally and administered intravenously or intramuscularly to treat intrahepatic cholestasis; toxic, viral, drug-induced, and alcoholic liver damage; cirrhosis, encephalopathy, including those in hepatic failure; depressive and abstinence syndrome.

Lipoic acid stimulates detoxifying function of liver, exhibits an antioxidant activity, participates in lipid and carbohydrate metabolism. The drug is prescribed to treat infectious hepatitis, chronic hepatitis, cirrhosis, intoxications, coronary atherosclerosis, and diabetic polyneuropathy.

Drugs Used to Dissolve Gallstones (Cholelitholytic Drugs)

It is proved, that certain derivatives of deoxycholic acid, such as *ursodeoxycholic acid* (*Ursofalk*) and *chenodeoxycholic acid* (*Chenofalk*) are able to dissolve cholesterol stones in gallbladder containing less than 4 % calcium. Intake of these drugs is accompanied by reduction of cholesterol concentration in bile. Chenodeoxycholic acid inhibits the synthesis of cholesterol in hepatocytes. Ursodeoxycholic acid decreases the intestinal absorption of cholesterol and suppresses its synthesis. Reduction of cholesterol concentration in bile decreases probability of stones formation in gallbladder. The change in ratio of cholesterol and bile acids in favor of the latter promotes gradual dissolution of

cholesterol-containing gallstones. These drugs are effective in case of long-time their intake (more than 1 year). Side effects of cholelitholytic drugs are increase of aminotransferase activity, diarrhea, and itching. Ursofalk is also used to treat biliary cirrhosis.

Drugs Influencing Gastric Motility

These drugs are divided into agents which increase gastric motility (prokinetics) and those which inhibit gastric motility.

Prokinetics include such drugs as *metoclopramide, cisapride, domperidone* (*Motilium*), etc. Prokinetics are used at delayed gastric emptying and at gastroesophageal reflux. Metoclopramide blocks peripheral and central D_2-dopaminergic receptors and activates $5HT_4$-serotoninergic receptors. Cisapride acts as $5HT_4$-serotoninergic receptor agonist and indirectly excites cholinergic receptors of intramural ganglia. Domperidone blocks peripheral D_2-dopaminergic receptors that improves peristaltics.

M-cholinoblocking drugs (*atropine, platyphyllin, metacinium*), ganglion blocking drugs (*benzohexonium, pirilene*), drugs blocking both M- and N-cholinoceptors of ganglia (*Buscopan, Pro-Banthine*), and myotropic spasmolytics (*papaverine, No-Spa*, etc.) are used to reduce gastric motility.

Emetic Drugs

Emetic drugs are *apomorphine, herb of thermopsis, root of ipecacuanha, copper sulfate,* and *zinc sulfate.*

Vomiting is complex reflex act with protective value which develops due to activation of vomiting (emetic) centre. Stimulants of vomiting centre convey impulses from the mucous membrane of stomach, intestine, and other internal organs; impulses from vestibular apparatus and the cortex (psychogenic vomiting), from visual, scents and taste analyzers, etc. But chemoreceptors of trigger zone are of principal importance in stimulation of vomiting. Trigger zone is located on the base of the fourth ventricle of cerebrum. Neuronal membranes of its chemoreceptors contain D_2-dopaminergic, $5\text{-}HT_3$-serotoninergic, and M_1-cholinergic

receptors. Excitation of these receptors results in stimulation of vomiting centre.

Certain chemical substances which are synthesized in disturbed metabolism in renal and hepatic failure or in toxemia of pregnancy, as well as number of drugs (opioid analgesics, digitalis, antitumoral agents) also are stimulants of chemoreceptors of trigger zone.

Apomorphine is an emetic drug with central action. The drug is a specific agonist of D_2-receptors. Apomorphine is used for elimination of poison from the stomach in cases when gastric lavage is impossible (for example, poisoning by mushrooms or by other foods, which do not pass through a tube, etc). Apomorphine is administered subcutaneously or intramuscularly. Emetic effect develops in 2–15 minutes.

Inducing vomiting is contraindicated to unconscious patients, pregnants, in childhood and advanced age, as well as in poisoning by gasoline, kerosene, turpentine, acids, alkalis, and other substances, affecting mucous membranes. In such cases, the gastric lavage with absorbents and the following saline laxatives is preferable.

Thermopsis herb and *ipecacuanha root* are agents which excite emetic centre reflexively. These drugs, taken orally in high doses, excite stomach receptors and stimulate vomiting by reflex mechanism. It should be noticed that alkaloids of thermopsis and ipecacuanha after absorption into the blood can directly stimulate the chemoreceptors of trigger zone.

Copper sulfate and *zinc sulfate* also have the peripheral mechanism of emetic action which is associated with irritation of mucous membrane of stomach.

It should be noted, that the use of emetic drugs in medical practice is significantly restricted.

Antiemetic Drugs

Antiemetic drugs are classified as follows.

1. Agents which are used to treat vomiting of central origin:

– antagonists of D_2-dopaminergic receptors: *metoclopramide, thiethylperazine, perphenazine (aethaperazinum), aminazine* (*chlorpromazine*), *triftazinum,* etc.;

– antagonists of 5-HT_3-serotoninergic receptors: *ondansetron, tropisetron, granisetron*.

2. Agents which are effective at vomiting due to violation of vestibular apparatus:

– M-cholinoblockering drugs: *scopolamine, "Aeron"*;

– antagonists of H_1-histaminergic receptors: *dimedrolum, diprazinum*.

At kinetosis (seasickness and airsickness), vomiting occurs due to overexcitation of vestibular apparatus. Vestibular apparatus carries out impulses to the cerebellum, which, in turn, transmits impulses to the vomiting centre. Because M-cholinergic and H_1-histaminergic receptors of cerebellum participate in this transduction of impulses, the following drugs are used to prevent vomiting of vestibular origin: tablets *"Aeron"* (contain M-cholinoblocking agents scopolamine and hyoscyamine), tablets or patch of *scopolamine* (*Scopoderm TTS*), and H_1-histaminergic antagonists – *dimedrolum* and *diprazinum*. These drugs are effective at kinetosis due to blockage of M-cholinergic and H_1-histaminergic receptors in cerebellum. But it is possible, that a direct inhibitory influence upon vomiting centre also participates in antiemetic effect of these agents. Their side effects include drowsiness, dry mouth, and blurred vision.

Metoclopramide (*Cerucal, Reglan*) is one of the most often used antiemetic drugs. Mechanism of its action is associated with the blockage of D_2-receptors in neurones of trigger zone. High doses of the drug block also 5-HT_3-serotoninergic receptors. Metoclapramide is used in the treatment for stomach and duodenum ulcer, meteorism, dyskinesia, oncological diseases of gastrointestinal tract, radiation sickness, uraemia, delayed gastric emptying, and reflux esophagitis. The drug is taken orally or administered

parenterally (intramuscularly or intravenously). Its effect develops quickly and lasts 6–8 hours. Side effects of metoclopramide include drowsiness, tinnitus, dry mouth, and extrapyramidal disorders typical for parkinsonism.

Certain neuroleptics – phenothiazine derivatives, such as *thiethylperazine, perphenazine (aethaperazinum), chlorpromazine (aminazine),* and *triftazinum* are also used as antiemetic agents. Their mechanism of action is associated with blockage of D_2-receptors of trigger zone. Thiethylpirazine also directly oppresses vomiting centre. Besides, these drugs exert marked sedative and antipsychotic effects. Neurileptics are effective in vomiting of central origin.

Ondansetron (*Zofran*), *tropisetron,* and *granisetron* are antagonists of 5-HT_3-serotoninergic receptors. Drugs are characterized by high efficacy in vomiting following cancer chemotherapy, in postoperative period, and in radiation sickness. Drugs are taken once a day orally or administered parenterally. Their antiemetic effect lasts to 24 hours. Side effects are headache, dizziness, and constipation.

Drugs Influencing Intestinal Motility

Drugs stimulating intestinal motility (Prokinetics)

This group includes drugs which elimanate intestinal atony.

According to mechanism of action, these drugs are classified as follows:

1) drugs stimulating M-cholinergic receptors: *aceclidine*;

2) cholinesterase inhibitors: *proserinum, pyridostigmine, distigmine*;

3) agonists of 5-HT_4-serotoninergic receptors: *cisapride*;

4) agonists of motilin receptors: *erythromycin, oleandomycin*.

Aceclidine interacts with M-cholinergic receptors of smooth muscles of gastrointestinal tract and excites them.

Cholinesterase inhibitors (*proserinum*, etc.) suppress the activity of cholinesterase and increase the level of acetylcholine in cholinergic synapses.

Motilin receptors are located in antrum and in duodenum. These receptors are excited by motilin. It is gastrointestinal polypeptide hormone which stimulates gastrointestinal motility. Antibiotics *erythromycin* and *oleandomycin* excite motilin receptors and stimulate intestinal motility.

Besides, such drugs as hormonal agent vasopressin and laxative drugs also stimulate intestinal smooth muscles.

Drugs Inhibiting Intestinal Motility and Reducing Intestinal Spasms

Following groups of drugs are used to eliminate intestinal spasticity:

1) M-cholinoblockers: *atropine, platyphyllin, metacinium*;

2) ganglion blockering drugs: *pirilenum, benzohexonium (hexamethonium)*;

3) myotropic spasmolytics: *papaverine, drotaverine (No-spa)*.

Pharmacology of M-cholinoblockering and ganglion blockering drugs is presented in relevant sections. Myotropic spasmolytics or myotropic antispasmodic agents inhibit the enzyme phosphodiesterase that leads to accumulation of cAMP and decrease of smooth muscles' tone and motility.

Antidiarrheal Drugs

Antidiarrheal drugs are used in the treatment for diarrhea. These drugs eliminate diarrhea by means of slowdown of intestinal peristalsis and contraction of its sphincters or by means of reduction of irritants influence upon intestinal mucosa. For pathogenetic therapy, drugs eliminating intestinal dysbiosis are used.

Diarrhea is due to different diseases and intoxications (psychogenic diarrhea, cholera, dysentery, poisoning by heavy metal salts and arsenicum, sharp change of feeding habits, insufficiency of

gastric or pancreatic secretion, etc.). Long-lasting diarrhea is dangerous by dehydration and loss of electrolytes that is accompanied by hypotension, disorders of conscious, convulsions, and other disorders.

Each disease, accompanied by diarrhea, needs specific therapy. Thus, chemotherapy is used to treat infectious enterocolitis. Substitutive therapy by pepsin, gastric juice, or pancreatic enzymes are used in the treatment for diarrhea due to insufficiency of gastric or pancreatic secretion. At dysbiosis, pathogenic microflora is eliminated by antibacterial drugs and patient receives probiotics and prebiotics.

Besides mentioned above drugs, nonspecific anti-inflammatory agents are used to treat diarrhea: enveloping, astringent, and absorbing drugs.

Astringent drugs are able to form protective film on the surface gastrointestinal mucosa. Due to this, astringents protect mucosa from irritation, reduce inflammation, accelerate epithelization of erosions and ulcers, and slow down peristalsis. The following astringent drugs are used to treat diarrhea: *albumin tannate (albutannin, tannalbin),* infusions or decoctions of *oak bark, Hypericum grass, blueberry fruits, bismuth subnitrate,* etc.

Albumin tannate is compound of tannin with casein. The drug exerts astringent action only in the intestine, because protein is degisted and tannin is released. Tannin itself exhibits astringent effect. Albutannin is taken orally 1–2 tablets 3–4 times a day.

Bismuth subnitrate exerts astringent and antibacterial effects.

Astringent drugs are used to treat inflammatory intestinal diseases. The drugs are prescribed alone or combined with antibacterial, spasmolytic, and enveloping drugs.

Enveloping drugs are high molecular weight substances which form colloids with water mechanically protecting gastrointestinal mucosa from irritants. It leads to decrease of intestinal peristalsis and reduces inflammation. *Starch slime, slime of flax seeds, slime of gum arabic,* etc. are used as enveloping drugs.

Activated carbon, diosmectite (Smecta) and other absorbing drug are used in the treatment for gastritis, meteorism, infectious gastrointestinal diseases, food toxicoinfection, and poisoning. Activated carbon is taken 1–2 g 3–4 times a day to treat meteorism. At acute poisoning, 20–30 g activated carbon is taken orally with the following intake of saline laxatives.

Loperamide (Imodium) is a phenylpiperidine derivative which stimulates μ-opioid receptors in the intestine and inhibits peristalsis. Besides, the drug increases tone of pyloric sphincter and exerts weak analgesic action. Antidiarrheal effect of loperamide lasts 4–6 hours.

Antiflatulent Drugs

Antiflatulent drugs are used in the treatment for meteorism. Antiflatulent drugs include preparations obtained from *Peppermint* leaves and *Chamomile* flowers.

Peppermint leaves contain etheric oils, carotene, flavonoids, polyphenols, sterols, microelements, and menthol. At application on mucous membranes or skin, menthol irritates cold-sensitive receptors and causes feeling of coldness. Excitation of cold receptors leads to contraction of superficial vessels and reflex relaxation of vessels of inner organs. This property of menthol is used to eliminate angina pectoris attacks. Also, menthol exerts mild local anaesthetic and antiseptic effects. In gastrointestinal tract, menthol irritates receptors of gastric and intestinal mucosa and activates their peristalsis and secretion. Besides, peppermint preparations stimulate bile secretion. Galenical preparations of peppermint exhibit antispasmodic action and inhibit putrefying in intestine.

Chamomile flowers contain flavonoids, dioxycumarins, choline, ascorbic acid, carotene, etheric oil, and other bioactive substances. Etheric oil of Chamomile exerts mild stimulating effect upon centres of medulla oblongata, activates contractile activity of myocardium, and dilates cerebral vessels. Besides, etheric oil of Chamomile stimulates bile secretion, reduce inflammation, and activate regeneration of epithelium. In high doses, etheric oil inhibits central

nervous system and decreases skeletal muscle tone. Galenical preparations of Chamomile are used as antiseptic, bile-expeling, diaphoretic, and antiflatulent drugs. Also, these drugs are used to treat gastric and intestinal pain, ulcers and different inflammatory diseases of gastrointestinal tract.

Laxative Drugs

Laxative agents are classified as follows:

1. Saline laxatives: *magnesium sulfate, sodium sulfate*.
2. Organic laxatives.

2.1. Drugs of plant origin:

– vegetable oils: *castor oil*;

– drugs contaning anthraquinone glycosides: *extract of buckthorn (Rhamnus cathartica) cortex, rhubarb (Rheum) root, senna leaves*.

2.2. Synthetic drugs: *isaphenine, phenolphthalein, sodium picosulfate (Guttalax), bisacodyl, Duphalac*.

3. Combined drugs: *Cafiolum* and *Regulax*.

Saline Laxatives

Magnesium sulfate and *sodium sulfate* are used to purificate both small and large intestines. These drugs create high osmotic pressure in intestine that causes the retention of water in the intestinal lumen. An increase of intestinal content volume results in distension of bowel and irritation of intestinal mechanoreceptors that increases peristalsis. Drugs act throughout small and large intestines. Saline laxatives are taken orally in dose 15–30 g with 1–2 glasses of water. Their effect develops in 2–3 hours and lasts up to 6 hours. These drugs are used at acute constipation and in the treatment for acute poisoning to prevent the absorption of toxins into the blood.

Vegetable Oils

Castor oil is extracted from castor seeds. In duodenum, castor oil is hydrolysed by pancreatic lipases to glycerin and ricinic acid. Ricinic acid irritates receptors and stimulates the peristalsis throughout small and large intestines. Besides, ricinic acid affects intestinal absorption of ions and water.

Castor oil is taken orally in dose 15–30 g for 30 minutes. Laxative effect develops in 2–6 hours. Castor oil is used at acute constipation, for preparation of a patient to roentgenologic examinations or to surgery on the abdominal organs. Also, castor oil may be used in the treatment for poisoning caused by lipid-insoluble toxins. It should be noticed that castor oil stimulates the uterine contractions.

Drugs Containing Anthraquinone Glycosides

These drugs increase the peristalsis and facilitate feces excretion. Extracts of *buckthorn cortex, rhubarb root,* and *senna leaves* are most commonly used drugs of this group. Natural vegetable anthraquinone glycosides lack laxative effect. But, under the influence of intestinal bacteries, these substances are hydrolyzed into anthraquinone derivatives, which irritate the intestinal receptors and stimulate peristalsis. These drugs act only in large intestine.

Drugs are taken orally once in 2–3 days, as a rule at the bedtime or in the morning before breakfast. Laxative effect develops in 8–10 hours.

Anthraquinone glycosides accumulate in the mucous membrane and smooth muscles of the bowels and can cause the atrophy of its smooth muscle layer. In this case constipation becomes chronic and resistant to laxative drugs. Long-lasting intake of these laxatives can cause hepatic dysfunction.

Synthetic Laxative Drugs

Phenolphthalein is absorbed into the small intestine and secreted into the large one, where it irritates receptors and decreases the absorption of electrolytes and water. Laxative effect develops in 6–8 hours after the drug intake. Phenolphthalein can cumulate in the body and affect the kidneys. Side effects of phenolphthalein include allergic reactions, intestinal colics, tachycardia, and collapse.

Mechanism of action of *isaphenine* is similar to phenolphthalein, but this drug is less toxic.

Sodium picosulfate (Guttalax) and *bisacodyl* under the influence of intestinal bacteries release the active radicals stimulating intestinal receptors and increasing peristalsis. The drugs are used to treat chronic constipations. Onset of their laxative effect is observed in 6–10 hours after drugs intake.

There are combined laxative drugs – *Cafiolum* and *Regulax*. These drugs are used in the treatment for chronic constipations.

Vaseline oil and other oils also exert laxative effect. Disaccharides (lactulose and sorbitol) soften contents of large intestine and increase its volume that stimulate peristalsis. Lactulose is an active component of *Duphalac*. Glycerin suppositories are also used for fast defecation. Glycerin irritates intestinal mucosa and stimulates contraction of rectum. Its effect develops in 15–20 minutes.

Table 6 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Desopimonum	Orally 0.025 g 2 times a day	Tablets 0.025 g
Succus gastricus naturalis	Orally 15–30 ml with meal	Vials 100 ml
Pepsinum	Orally 0.2–0.5 g with meal	Powder
Acidum chidrochloricum dilutum	Orally 10–15 drops with meal	Vials 50 ml
Ranitidinum	Orally 0.15 g 2–3 times a day	Tablets 0.15 g

Continuation of the table 6

Drug name (Latin)	Single dose and route of administration	Drug product
Pirenzepinum	Orally 0.05 g 2 times a day; intravenously or intramuscularly 0.01 g 2 times a day	Tablets 0.025 or 0.05 g; ampoules 2 ml of 0.5 % solution
Omeprazolum	Orally 0.02 g once a day	Capsules 0.02 g
Magnesii oxydum	Orally 0.25–1.0 g 4 times a day	Powder; tablets 0.5 g
Almagelum	Orally 1 teaspoon 4 times a day	Vials 150 ml
De-nolum	Orally 0.12 g 4 times a day	Capsules 0.12 g
Sucralfatum	Orally 0.5–1 g 4 times a day	Tablets 0.5 or 1.0 g
Apomorphini hydrochloridum	Subcutaneously 0.002–0.005 g	Ampoules 1 ml of 1 % solution
Metoclopramidum	Orally 0.01–0.02 g 2–3 times a day; intramuscularly or intravenously 0.01 g 1–3 times a day	Tablets 0.01 g; ampoules 2 ml of 0.5 % solution
Aethaperazinum	Orally 0.004–0.006 g 3–4 times a day	Tablets 0.004 or 0.006 g
Cholenzymum	Orally 1 tablet 1–3 times a day after a meal	Combined tablets containing 0,1 g dry bile, 0,1 g dried pancreatic gland, and 0,1 g dried mucous membrane of the small intestines
Cholosasum	Orally 1 teaspoon 2–3 times a day after a meal	Vials 50 or 300 ml
Papaverini hydrochloridum	Orally 0.04–0.06 g 3–4 times a day; subcutaneously, intramuscularly or intravenously 0.02–0.04 g	Tablets 0.04 g; ampoules 2 ml of 2 % solution
Nospanum	Orally 0.04–0.08 g 2–3 times a day; subcutaneously, intramuscularly or intravenously 0.04–0.08 g	Tablets 0.04 g; ampoules 2 ml of 2 % solution

Continuation of the table 6

Drug name (Latin)	Single dose and route of administration	Drug product
Oxaphenamidum	Orally 0.25–0.5 g 3 times a day after a meal	Tablets 0.25 g
Pancreatinum	Orally 0.25–0.5 g 3 times a day during or after a meal	Tablets 0.25 or 0.5 g
Magnesii sulfas	Orally 10–30 g in 1 glass of water	Powder
Oleum Ricini	Orally 15–30 g	Capsules 1.0 g
Isapheninum	Orally 0.005–0.01 g 1–2 times a day	Tablets 0.01 g
Contrical	Intravenously drop-by-drop 10 000–50 000 IU	Vials 10 000, 30 000 or 50 000 IU of powder for injection

Step 1. Tasks for Self-Control
Drugs Influencing Digestive System

1. A 37-year-old man was admitted to the surgical department with symptoms of acute pancreatitis: vomiting, diarrhoea, bradycardia, hypotension, weakness, dehydration of the organism. What medicine should be used first?

A. No-spa.
B. Contrical.
C. Etaperazine.
D. Ephedrine.
E. Platyphyllin.

2. Cimetidine slows metabolism of many drugs because it inhibits the activity of:

A. Phase II glucuronidation reactions.
B. Monoamine oxidase (MAO).
C. Cytochrome P-450.
D. H^+, K^+-ATPase.
E. Tyrosine kinase.

3. The absorption of phosphate reduces when large and prolonged doses of which of the following antacids are given?

A. Calcium carbonate.

B. Magnesium hydroxide.

C. Magnesium trisilicate.

D. Sodium bicarbonate.

E. Sucralfate.

4. Omeprazole, an agent for the promotion of peptic ulcers tretment, has a mechanism of action that is based on:

A. Anticholinergic action.

B. Gastric secretion.

C. Pepsin secretion.

D. Prostaglandins.

E. H^+, K^+-ATpase.

5. The approved indication for misoprostol is:

A. Pathologic hypersecretory conditions such as Zollinger-Ellison syndrome.

B. Regional ileitis.

C. Ulcerative colitis.

D. Reflux esophagitis.

E. Prevention of gastric ulceration in patients using large doses of aspirin-like drugs.

6. Bismuth salts are thought to be effective in peptic ulcer disease because they have bactericidal properties against:

A. Staphylococcus aureus.

B. Helicobacter pylori.

C. Clostridium difficile.

D. Escherichia coli.

E. Bacteroides fragilis.

7. Misoprostol has a cytoprotective action on the gastrointestinal mucosa because it:

A. Coats the mucosa.

B. Neutralizes acid secretion.

C. Antagonizes nonsteroidal anti-inflammatory drugs.

D. Enhances secretion of mucus and bicarbonate ion.

E. Relieves ulcer symptoms.

8. Point out the primary pharmacological effect of omeprazole:

A. Reduction of secretion of intrinsic factor.

B. Reduction of gastric motility.

C. Stimulation of secretion of pepsin.

D. Elevation of volume of gastric juice.

E. Reduction of secretion of hydrochloric acid.

9. Which of the following is not associated with sucralfate?

A. It has moderate acid-neutralizing properties.

B. It maintains gel-like qualities even at acid pH.

C. It binds to ulcer craters more than to normal mucosa.

D. It contains polyaluminium hydroxide.

E. It reacts little with mucin.

10. Point out the preferred drug for therapy of Zollinger-Ellison syndrome:

A. Metronidazole.

B. Sucralfate.

C. Omeprazole.

D. Ranitidine.

E. Misoprostol.

11. A 36-year-old woman with severe erosive esophagitis is prescribed pantoprazole. Which of the following side effects of such therapy is one of the most common?

A. Headache.

B. Constipation.

C. Vomiting.

D. Heartburn.

E. Paresthesias.

12. While taking non-steroidal anti-inflammatory drug for arthritis, a 65-year-old man developed gastric ulcer. He was prescribed ranitidine for 8 weeks. This drug binds a receptor located in the:

A. Cell wall.

B. Nucleolus.

C. Cytoplasm.
D. Cell membrane.
E. Nucleus.

13. Gastric acid secretion is stimulated by the presence of:
A. Acetylcholine and pepsin.
B. Histamine and motilin.
C. Norepinephrine and gastrin.
D. Norepinephrine and histamine.
E. Gastrin and acetylcholine.

14. A physician must always be aware of possible drug interactions. Aluminum hydroxide antacids tend to interfere with the gastrointestinal absorption of:
A. Cephalexin.
B. Tetracycline.
C. Erythromycin.
D. Chloramphenicol.
E. Penicillin G.

15. One mechanism to reduce gastric acid secretion is by blocking the H^+, Na^+-ATPase pump in the parietal cell. One drug that has this pharmacologic action is:
A. Omeprazole.
B. Pirenzepine.
C. Misoprostol.
D. Serotonin.
E. Isoniazid.

16. Concomitant administration of calcium and/or magnesium antacids to patients receiving one of the tetracycline drugs may have the following effects upon the action of the tetracycline:
A. Suppresses hypersensitivity reactions.
B. Decreases the action.
C. Enhances the action.
D. Increases toxicity.
E. Causes no significant change.

17. Famotidine is prescribed to a patient with gastric ulcer. The acidity of gastric juice has considerably decreased. What mechanism underlies the action of the drug?

A. Blockade of N-cholinoceptors.

B. Blockade of H_1-histaminic receptors.

C. Blockade of M_1-cholinoceptors.

D. Suppression of Na^+, K^+-ATPase activity.

E. Blockade of H_2-histaminic receptors.

18. A 40-year-old patient suffers from gastric ulcer at the stage of exacerbation accompanied by a substantial increase of the acidity of gastric juice, pain, and dyspeptic syndrome. Choose the drug for treatment of this patient.

A. Festal.

B. Allocholum.

C. Famotidine.

D. No-spa.

E. Papaverine hydrochloride.

19. A patient complains of stomachache and heartburn. Tests revealed the increase of gastric juice acidity. What drug should be prescribed to the patient for neutralization of the excessive acidity of gastric juice?

A. Benzohexonium.

B. Almagel.

C. Papaverine hydrochloride.

D. Ranitidine.

E. Atropine.

20. In a patient with stomach ulcer *Helicobacter pylori* were detected. What drug, which influences *Helicobacter pylori*, should be prescribed in this case?

A. Maalox.

B. Almagel.

C. Famotidine.

D. Metronidazole.

E. Atropine sulfate.

21. To a patient with ulcer disease of stomach was prescribed drug, the mechanism of which action is based on the blockade of H_2-hystamine receptors. Call this drug.

A. Dithylinum.

B. Bisacodyl.

C. Omeprazole.

D. Atropine sulfate.

E. Famotidine.

22. A patient suffering from chronic hyperacidic gastritis takes an antacid drug for heartburn elimination. After its ingestion the patient feels better but at the same time, he has a sensation of stomach swelling. Which of the following drugs might be the cause of such side effect?

A. Aluminium hydroxide.

B. Sodium hydrocarbonate.

C. Magnesium oxide.

D. Magnesium trisilicate.

E. Pepsin.

23. Metoclopramide has antiemetic properties because it:

A. Decreases gastric secretion.

B. Lowers esophageal sphincter pressure.

C. Accelerates gastric emptying time.

D. Has sedative properties.

E. Is a central nervous system dopamine-receptor antagonist.

24. Point out the drug to treat steatorrhea of pancreatic insufficiency:

A. Secretin.

B. Misoprostol.

C. Pancrelipase.

D. Cimetidine.

E. Bile salts.

25. A 20-year-old woman goes to the emergency department, stating that within the past hour she ingested “a handful of sleeping

pills". She is still awake. Which of the following drugs can be given to induce vomiting?

A. Apomorphine hydrochloride.
B. Metoclopramide.
C. Morphine.
D. Promethazine.
E. Ondansetron.

26. A 62-year-old woman on haemodialysis is scheduled for a screening colonoscopy. Which drug should be prescribed for her colonic preparation?

A. Cholosasum.
B. Omeprazole.
C. Magnesium oxyde.
D. Magnesium sulfate.
E. Ranitidine.

27. A 37-year-old man was admitted to the surgical department with symptoms of acute pancreatitis: vomiting, diarrhoea, bradycardia, hypotension, weakness, dehydration of the organism. What medicine should be used first of all?

A. Contrical.
B. Platyphyllin.
C. Etaperazine.
D. Ephedrine.
E. No-spa.

28. A 48-year-old woman receives epidural anaesthesia for vaginal hysterectomy. In recovery room, a fentanyl infusion was begun epidurally for relief of postoperative pain. About six hours later, she began to complain of nausea and had two episodes of vomiting. How could nausea and vomiting best be relieved?

A. Administer apomorphine.
B. Sedate the patient with midazolam (versed).
C. Withhold oral administration of fluids.
D. Discontinue the fentanyl (sublimaze) infusion.
E. Administer ondansetron.

29. In esophagitis, elevation of the head of the bed, abstinence from ethanol and tobacco, and small frequent meals are all useful adjunctive therapeutic measures. Other useful therapy may include all of the following except:

A. Amitriptyline.

B. Metoclopramide.

C. Bethanechol.

D. Cimetidine.

E. Omeprazole.

30. An ambulance took a patient to a hospital in serious condition (nausea, vomiting). It is established that the day before he celebrated a wedding with the family. The initial diagnosis is food toxicoinfection. What drug is it necessary to use first of all?

A. Adrenaline hydrochloride.

B. Butamide.

C. Clophelinum.

D. Dimedrol.

E. Magnesium sulfate.

31. Intestine colic has developed in hypertensive patient. Choose the drugs group which is most rational for interruption of colic in this patient.

A. Adrenomimetics.

B. Miotropic spasmolytics.

C. Sympathomimetics.

D. M-cholinoblockers.

E. Cholinesterase inhibitors.

32. Laxative drug having osmotic activity was prescribed to patient. What is this drug?

A. Sustac.

B. Bisacodyl.

C. Vaseline.

D. Isaphenine.

E. Magnesium sulfate.

33. Laxative drug was prescribed to patient with brain edema. Indicate this drug.

A. Liquid paraffin.
B. Cortex of buckthorn.
C. Magnesium sulfate.
D. Castor oil.
E. Bisacodyl.

DIURETIC DRUGS

Diuretics are drugs which increase the excretion of salts and water from the body. These drugs are also referred as "saluretics" because their mechanism of action is associated with the ability to increase excretion of sodium and chlorine ions. Diuretics are widely used in medicine, including the emergency treatment. Various renal, cardiovascular, and hepatic diseases and some other pathological states are accompanied by retention of salts and water that leads to the increase of tissues hydratation, development of edemas, and accumulation of fluids in body cavities.

Mechanism of diuretics action can be understood based on the modern ideas about process of diuresis. About 150–200 *l* of fluid and 25 000 milliequivalents of sodium are filtrated in human kidneys for 24 hours. But up to 99 % of initial urine undergoes reabsorption and only 2 *l* of fluid and 100 milliequivalents of sodium are excreted with urine. Initially, sodium reabsorption from the renal tubules occurs through apical membrane. Sodium is transported through apical membrane by means of special carrier protein which is synthesized under control of aldosterone. After entering in the cells of renal tubules, sodium ions are absorbed through basal membrane in the interstitium and capillaries. Sodium transport through basal membrane is an active process that occurs by means of special pumps. These pumps transport sodium ions against concentration gradient with energy consumption. There are pump transporting sodium ions in exchange for potassium ions and pump transporting sodium ions together with chlorine or hydrocarbonate ions

independently of potassium. Reabsorption of water is a passive process dependent on sodium reabsorption. Resynthesis of ATP is provided due to oxidative phosphorylation in renal cortex and due to glycolysis – in renal medulla. Sodium transport through intercellular spaces is also important part of reabsorption. Sodium is pumped by lateral cellular surfaces into channels, which are cloused from the direction of apical membrane but are opened from the direction of basal membrane. Increased sodium concentration in these intercellular spaces leads to water flow from channel in the peritubular capillaries. Intercellular spaces create the necessary conditions for flow of water and sodium ions from peritubular space into channel that is very important.

In different segments of nephron, a degree of resistance of channel wall for water reabsorption is different. Descending part of Henle's loop is easily permeable for water, whereas ascending segment is permeable for sodium and chlorine ions and poorly permeable for water. Urine becomes hyposmotic due to passing through ascending segment. But interstitial fluid in renal medulla becomes hyperosmotic that promotes the reabsorption of water in descending part of Henle's loop. Final urine formation is occurred in distal convoluted tubules and collecting ducts.

Transport of sodium ions and water is under hormonal control. Vasopressin (antidiuretic hormone) controls water retention in the body. Mineralocorticoid aldosterone stimulates sodium reabsorption and simultaneous secretion of potassium through apical membrane of nephron by electrochemical gradient. Renal sodium transport is also regulated by natriuretic peptide which secreted by atriums, hypothalamus, and liver. Such hormones as estrogens, somatotropin, and insulin increase sodium reabsorption. Progesterone, parathyroidin, and glucagon inhibit sodium reabsorption. Some biologically active local agents synthesized in kidneys also are important (e. g., kinins, prostaglandins, dopamine).

Based on the characteristics of the process of urine formation, it is evident that diuretics can either directly influence uropoiesis or change hormonal regulation of this process.

There are numerous classifications of diuretics. Classification based on the action mechanism of diuretics and localization of their action is given below.

1. Diuretics acting on the level of epithelial cells of renal tubules and inhibiting sodium and water reabsorption.

1.1. Diuretics acting on the level of basal membrane:

a) derivatives of anthranilic and benzoic acids: *furosemide, torasemide (torsemide),* and *bumetanide (Bufenox)*;

b) benzamide derivatives: *clopamide* and *indapamide*;

c) benzothiadiazine derivatives (thiazides): *dichlothiazidum (hydrochlorothiazide), cyclomethiazide,* and *polythiazide*;

d) derivatives of dichlorophenoxyacetic acid: *etacrynic acid (ethacrynic acid)*;

e) carbonic anhydrase inhibitors: *acetazolamide (diacarb)*.

1.2. Diuretics acting on the level of apical membrane – drugs inhibiting transporters of sodium: *triamterene, amiloride*.

2. Aldosterone antagonists: *spironolactone*.

3. Osmotic diuretics: *mannitol*.

4. Drugs increasing renal circulation: *euphyllinum (aminophylline)*.

5. Diuretics of plant origin: *horsetail herb, bearberry leaves, birch buds*, etc.

Depending on the efficacy of diuretic activity, all drugs are classified as follows:

1. Most effective diuretics: *furosemide (Lasix), etacrynic acid (Uregyt), clopamide (Brinaldix), mannitol.*

2. Diuretics with moderate activity: *dichlothiazidum, cyclomethiazide, polythiazide, hlortalidone (oxodolinum, Hygroton)*.

3. Diuretics with weak activity: *diacarb, spironolactone (Verospiron, Aldactone), triamterene, amiloride, euphyllinum, drugs of plant origin*.

Depending on speed of effect development, diuretics are classified as follows:

1. Diuretics with fast development of the effect (within 30–40 minutes): *furosemide, etacrynic acid, mannitol, bumetanide, torasemide*.

2. Drugs with a moderate speed of the effect development (onset of action is in 1–4 hours after drug administration, and duration of the action is 9–24 hours): *dichlothiazidum, diacarb, euphyllinum, cyclomethiazide, clopamide, chlortalidone , triamterene, indopamide*.

3. Diuretics with slow development of the effect (onset of action is in 2–5 days after drug intake, and duration of action is 5–7 days): *spironolactone, potassium canrenoate*.

Diuretics Acting on the Level of Epitelial Cells of Renal Tubules

Derivatives of Antranilic and Benzoic Acids (Loop Diuretics)

Furosemide (Lasix), torasemide (Trifas), bumetanide (Bufenox) inhibit hexokinase, malate dehydrogenase, succinate dehydrogenase, and Na^+, K^+-ATPase. Besides, these drugs dissociate energy production and its supply to the ionic pumps. These changes cause the reduction of sodium current through basal membrane in intersticium. Also, loop diuretics increase the synthesis of prostaglandins and kinins which dilate renal vessels and increase sodium excretion.

A main segment of these drugs action is a thick ascending limb of the Henle's loop; therefore, these drugs are referred as "loop diuretics". In certain degree, anthranilic acid derivatives inhibit sodium reabsorption in proximal tubules.

All agents of this group increase potassium excretion that is undesirable. It is due to the increase of luminal membrane permeability for sodium ions in distal convoluted tubules that is accompanied by the increase of intratubular potencial and elevation of passive potassium secretion into the tubular lumen.

Furosemide (Lasix) was introduced in medical practice in 1963. The drug exerts marked diuretic effect both at parenteral and enteral administration. At oral intake, its effect develops in 30–60 minutes and lasts 6–8 hours. At intravenous administration, furosemide's effect develops in 5–10 minutes and lasts 2–4 hours.

Furosemide is readily absorbed from gastrointestinal tract and binds with plasma proteins. Furosemide undergoes hepatic metabolism through hydrolysis and conjugation with glucuronic acid. Metabolites are excreted by kidneys.

Furosemide is a low toxic agent with therapeutic dosage range from 0.002 g to 2.0 g. It is one of the most potent diuretics. Furosemide is used in the treatment for chronic oedemas of cardiac, renal, and hepatic origin; acute heart failure, pulmonary oedema, brain oedema, acute and chronic renal failure, forced diuresis, hypertensive disease, and hypertensive crisis.

At hypertensive disease, therapeutic effect of furosemide is mainly result of the decrease of sodium concentration in the arteriole walls, and only partially is a result of circulatory volume decrease. Reduction of sodium concentration in vascular wall leads to the decrease of vascular sensitivity to vasoconstrictors.

Side effects of furosemide are hypokalemia, hypochloraemic alkalosis, hyperglycemia (due to reduction of pancreatic insulin secretion), hyperuricemia (furosemide competes with uric acid for binding with special carrier protein in proximal convoluted tubules), hypocalcemia, hypomagnesemia, hyperreninemia, ototoxicity (due to intravenous administration of high doses of furosemide).

Torasemide acts longer than furosemide and is presribed once a day.

Bumetanide (Bufenox) acts faster than furosemide. Its diuretic effect is 20–50 times higher than furosemide. Duration of bumetanide action is 4–6 hours. The drug is administered parenterally or taken orally. Indications for use and side effects are like furosemide. Its therapeutic indications and side effects are same with those of furosemide. But bumetanide causes less hypokalemia

than furosemide. Long-lasting therapy with bumetanide can cause muscular pain.

Benzamide Derivatives

Pharmacological properties of *clopamide* are like to those of furosemide. Clopamide exerts high natriuretic activity. The drug is taken orally. Onset of its diuretic effect is 1–3 hours. Duration of action is 8–20 hours.

Indapamide (Arifon) exerts diuretic and hypotensive effects. Its chemical structure is similar to those of clopamide. The drug is taken orally once a day in the morning. Indopamide is used predominantly to treat hypertensive disease.

Benzothiadiazine Derivatives (Thiazides)

Hydrochlorothiazide (dichlothiazidum) exerts moderate diuretic activity. The drug inhibits sodium and chlorine reabsorption mainly in initial part of distal convoluted tubules. Partly, its effect appears in proximal convoluted tubules. Hydrochlorothiazide is effective both in orall and parenteral administration; but practically, it is used mainly for orall intake. Its diuretic effect develops in 30–60 minutes after intake and lasts 8–12 hours. About 60 % taken dose binds to plasma proteins. Hydrochlorothiazide is excreted through kidneys. Development of tolerance is uncharacteristic of dichlothiazidum. Hydrochlorothiazide is used to treat oedemas due to chronic cardiac, hepatic and renal diseases; hypertensive disease, diabetes insipidus, and nephrolithiasis.

Mechanism of dichlothiazidum action in diabetes insipidus is the following. The drug inhibits phosphodiesterase in cells of renal medulla that that leads to accumulation of intracellular cAMP. Owing to this, the water reabsorption through epithelium of collecting ducts is increased. Volume of urina is reduced. That is, dichlothiazidum potentiates or restores the effect of vasopressin in patients with diabetes insipidus.

Most common side effects of hydrochlorothiazide are hypokalemia and hypochloraemic alkalosis. Hypomagnesemia,

hypercalcemia (due to increase of parathyroid hormone activity in kidneys), hyperuricemia, and hyperglycemia are also possible.

Pharmacological properties and therapeutic indications of *polythiazide* and *cyclomethiazide* are similar to those of dichlothiazidum. But, their diuretic activity is higher than activity of dichlothiazidum (polythiazide – 50 times, cyclomethiazide – 100 times).

Chlortalidone (oxodolinum) is like to thiazides. The drug is characterized by long duration of action. After oral intake onset of its action is in 2–4 hours, duration of effect is about 3 days.

Derivatives of Dichlorophenoxyacetic Acid

Etacrynic acid (Uregyt) is dichlorophenoxyacetic acid derivative. According to mechanism of action, this drug is a loop diuretic. The agent suppresses the reabsorption of sodium and chlorine ions on the level of basal membrane of epithelial cells in the thick ascending limb of the Henle's loop. Diuretic effect of etacrynic acid is high. Etacrynic acid is administered parenterally and orally. At oral intake, its effect develops in 30–60 minutes and lasts up to 8 hours. At intravenous administration, the effect develops in 5–15 minutes and lasts 3–4 hours.

Therapeutic indications for etacrynic acid are chronic oedemas of cardiac, renal, and hepatic origin, acute heart failure, pulmonary oedema, brain oedema, acute and chronic renal failure, forced diuresis, treatment of hypertensive disease, and interruption of hypertensive crisis.

Etacrynic acid exerts higher toxicity than furosemide. Its side effects are hypokalemia, hyponatremia, hypomagnesemia, hypochloremic alkalosis, hypocalcemia, hearing impairment, weakness, dizziness, diarrhea, etc. Intravenous administration of etacrynic acid is painful and can cause phlebitis.

Carbonic Anhydrase Inhibitors

Diacarb (acetazolamide) is a weak diuretic which inhibits carbonic anhydrase of epithelial cells in proximal convoluted tubules. This enzyme catalizes the synthesis of carbonic acid from water and carbon dioxide: $H_2O + CO_2 \rightarrow H_2CO_3$. Carbonic acid dissociates to hydrogen and hydrocarbonate ions. Kidneys secrete the hydrogen ions into urine with reabsorption of the hydrocarbonate ions. This process provides support of an acid-based balance in the body. Diacarb decreases reabsorption of the hydrocarbonate ions that leads to the increase of urine pH and reduces alkaline reserve of the blood. Retention of hydrogen ions is accompanied by compensatory secretion of potassium ions. Therapy with diacarb quickly leads to acidosis due to hyperchloremia.

Diacarb inhibits activity of ciliary body of the eye that decreases secretion of aqueous humor. Inhibition of carbonic anhydrase also leads to the decrease production of cerebrospinal fluid and reduction of intracranial pressure.

Effect of orally taken diacarb develops in 1–1.5 hours and lasts 6–12 hours. The drug is used in the treatment for alkalosis, exacerbation of glaucoma, glaucomatous crisis, intracranial hypertension, epilepsy, and poisoning by barbituric acid derivatives (increase of urine pH promotes renal excretion of barbiturates).

Main side effects of diacarb are acidosis and hypokalemia.

Diuretics Acting on the Level of Apical Membrane

Drugs Inhibiting Proteins Which Transport Sodium

Triamterene and *amiloride* are weak diuretics. These drugs inhibit the passive transport of sodium ions through apical membrane of epithelial cells into the distal convoluted tubules and collecting ducts. The agents interact both with sodium transport proteins and sodium channels. Triamterene and amiloride inhibit renal potassium secretion and, therefore, are referred as “potassium-sparing diuretics”. Both drugs are taken orally. Effect develops in 15–20 minutes after drug intake and lasts up to 12 hours.

These drugs are used in long-lasting maintenance therapy of chronic cardiovascular failure of various genesis, in the treatment for hypertensive disease and cirrhosis. Besides, potassium-sparing diuretics are widely used in combination with thiazides or loop diuretics to prevent hypokalaemia.

Side effects of potassium-sparing diuretics are hyperkalaemia, nausea, vomiting, headache, muscular convulsions of muscles of the lower extremities.

Aldosterone Antagonists

Chemical structure of potassium-sparing diuretic *spironolactone (Aldactone, Verospiron)* is similar to aldosterone. Spironolactone binds with intracellular cytoplasmic receptors of aldosterone and prevents its transport to the nucleus and following interaction with nuclear chromatin. It results in the decrease of synthesis of sodium transporting proteins – permease. Owing to such mechanism spironolactone decreases the aldosterone-dependent sodium reabsorption and potassium secretion in collecting ducts of nephron.

Diuretic effect of spironolactone develops in 2–5 days after therapy initiation and lasts several days after cessation of the drug intake.

Spironolactone is used in the treatment for chronic heart failure, liver cirrhosis, nephrotic syndrome, essential hypertension in adults, ascites, and hyperaldosteronism. Also, the drug is used in combination with other diuretics to prevent hypokalaemia.

Side effects of spironolactone include dizziness, drowsiness, headache, ataxia, nausea, vomiting, diarrhea, hepatic disfunction, gynecomastia, menstrual disorders, urticaria, hyperkalemia, etc.

Osmotic Diuretics

Mannitol exerts pronounced diuretic action and weak saluretic effect. The drug is readily filtered in renal glomerulus but is not reabsorbed from the primery urine. Thereby mannitol creates high osmotic pressure in tubular lumen and significantly decreases the

water reabsorption. Reduction of sodium concentration in the tubular lumen creates concentration gradient of sodium between the intersticium and tubular lumen. According to this concentration gradient, sodium ions move through intercellular spaces into the tubular lumen.

Mannitol increases the osmotic pressure of the blood that promotes water entering the blood vessels and the increase of circulatory volume. Hypervolemia activates secretion of atrial natriuretic peptide which stimulates natriuresis.

The drug is administered slowly intravenously. Diuretic effect develops in 10–15 minutes and lasts 4–6 hours.

Mannitol is used as to treat acute oedemas of brain and lungs, glaucoma, acute poisonings (for forced diuresis), acute renal failure, and shocks with decrease of blood pressure. It should be noticed that dehydrating therapy is dangerous in patients with heart failure. Elevation of blood osmotic pressure results in hypervolemia, particularly in patients with concomitant renal failure. The increase of pulmonary circulation pressure and systemic blood pressure can cause the overload of the left ventricle and development of pulmonary oedema.

Therapy with mannitol can be aggravated by dehydration, hyponatremia, impaired consciousness, nausea, vomiting, dizziness, and chest pain. The drug is not recommended to prescribe children under 1 year.

Drugs Increasing the Renal Blood Supply

Aminophylline (euphyllinum), theophylline, and *theobromine* increase diuresis due to improving of renal perfusion and glomerular filtration. Besides, drugs mildly reduce sodium reabsorbtion in proximal convoluted tubules. These effects are based on the ability of methylxanthines to stimulate purinergic (adenosine) receptors and to inhibit the phosphodiesterase activity that leads to accumulation of cAMP and reduction of vasopressin activity.

Methylxanthines are weak diuretics. These drugs are used to treat chronic cardiac, hepatic and renal diseases with insignificant oedemas in elderly patients.

It should be noticed that children are especially sensitive to methylxanthines. Intravenous administration of these drugs to them can provoke severe poisoning. Due to this, methylxanthines are contraindicated to children under 2 years.

Diuretics of Plant Origin

Herbal diuretics occupy a special position among diuretics. These agents are used in the form of infusions and broths. The following herbal agents are used as diuretics: *leaves of bearberry, leaves of orthosiphon stamineus, leaves and buds of birch, horsetail herb, flowers of cornflower*, etc. These drugs exert mild diuretic activity. Herbal diuretics are prescribed to children and elderly patients with oedemas caused by cardiovascular, hepatic, and inflammatory renal diseases. These drugs are taken 3–4 times a day. Therapy with herbal diuretics does not result in disorders of electrolyte balance.

Lespenephryl is a drug which is derived from leaves and stems of *Lespedeza capitata* and *Pimpinella anisum* (anise) fruit. The drug increases diuresis, excretion of nitrogenous compounds, and excretion of sodium and potassium ions. Lespenephryl is used to reduce azotemia at renal failure, acute and chronic nephritis. The drug is also used to reduce extrarenal azotemia. Lespenephryl is taken orally in a dose of 1–2 teaspoons a day. In severe cases, a daily dose may be increased up to 6 teaspoons. For long-lasting maintenance therapy, Lespenephryl is taken in dose 0.5–1 teaspoon alternate day.

Lespeflan (extract of *Lespedezae bicoloris*) is a similar drug with Lespenephryl. The drug is taken in a dose of 1 teaspoon or 1 tablespoon 3–4 times a day. A course of treatment lasts 3–4 weeks. Lespeflan is contraindicated in pregnancy.

Principles of Combined Diuretics Treatment

Diuretics are often combined among themselves as well as with agents of other groups to treat chronic heart failure, renal failure, hypertensive disease, etc.

Diuretics with different mechanisms of action are commonly combined to increase sodium and water excretion from the body. Thus, osmotic diuretic mannitol is combined with loop diuretics (furosemide, etacrynic acid). This combination is used in urgent therapty (forced diuresis at poisoning, acute brain oedema, etc.).

Combination of diuretics acting on the level of basal membrane (furosemide, hydrochlorothiazide, etc.) with diuretics which affect apical membrane (spironolactone, triamterene, etc.) is often used in medicine. Such combination increases the efficacy of diuretics and prevents the hypokalemia. Phrmaceutical industry manufactures such co-formulated drugs as "*Triampur Compositum*" (triamterene and hydrochlorothiazide), "*Moduretic*" (amiloride and hydrochlorothiazide), etc.

Diuretics are commonly combined with hypotensive agents to treat hypertensive disease. There are the following co-formulated drugs: "*Tenoric*" (β-adrenergic antagonist atenolol and diuretic chlorthalidone), "*Enap-H*" (angiotensin-converting enzyme inhibitor enalapril and hydrochlorothiazide), "*Crystepin*" (sympatholytic reserpine, clopamide, and α-adrenoblocker dihydroergocristine), etc.

Potassium-sparing diuretics (spironolactone, triamterene) are used together with cardiac glycosides to prevent hypokalemia.

It should be noticed that some diuretics can enhance toxicity of other drugs. Thus, furosemide and etacrynic acid increase ototoxicity of some antibiotics (gentamicin, etc.).

DRUGS INFLUENCING MYOMETRIUM

Uterus is a smooth muscle organ which is under control of certain hymoral and nervous factors. There are M-cholinergic, α- and β-adrenergic receptors in myometrium. M-cholinergic and α-adrenergic receptors stimulate contractile activity of uterus, while β_2-adrenergic receptors inhibit it. Expressed stimulating influence upon uterus is characteristic of estrogens, posterior pituitary hormone oxytocin, and prostaglandins E_2 and $F_{2\alpha}$. Progestins (progesterone, etc.) inhibit the uterine contractile activity.

Drugs influencing myometrium are classified as follows.

1. Drugs stimulating uterine contractile activity.

1.1. Drugs of oxytocin group: *oxytocin, demoxytocin (desaminooxytocin, Sandopart), methyloxytocin (mesotocin),* and *pituitrinum.*

1.2. Drugs of prostaglandin group: *dinoprost (prostaglandin $F_{2\alpha}$), methyldinoprost,* and *dinoprostone (prostaglandin E_2).*

1.3. Estrogens: *estron, estradiol,* and *sinestrol.*

1.4. β-adrenoblockers: *propranolol (anaprilinum).*

1.5. Miscellaneous drugs: *proserinum, pachycarpine, castor oil, calcium chloride, quinine, vitamins C and B_1.*

2. Drugs inhibiting uterine tone and contractile activity (tocolytics).

2.1. Drugs stimulating β_2-adrenergic receptors: *fenoterol (Partusisten), salbutamol (Salbupart),* and *terbutaline (Bricanyl).*

2.2. General anaesthetics: *oxybutyrate sodium.*

2.3. Hormonal drugs: *progesterone.*

2.4. Miscellaneous drugs: *magnesium sulfate.*

3. Drugs increasing uterine tone and accelerating uterine involution in postpartum period.

3.1. Ergot alkaloids: *ergotal, ergotamine, ergometrine, methylergometrine,* and *ergot extract.*

3.2. Synthetic drugs: *cotarnine.*

4. Drugs decreasing tone of uterine neck: *atropine, dinoprost,* and *dinoprostone*.

Drugs Stimulating Contractile Activity of Uterus

Oxytocin and prostaglandins are physiological stimulants of uterine contractions. The membranes of uterine smooth muscle cells contain receptors which are sensitive to these substances. Their excitation activates entrance of sodium and calcium ions into the cells that leads to depolarization and contraction of smooth muscle cells. Oxytocin and prostaglandins are allowed for in-patients only.

Drugs of Oxytocin Group

Oxytocin is a polypeptide hormone of posterior pituitary which consists of 8 amino acids. The drug in doses 3–5 units causes the rhythmic contraction of myometrium that promotes labor. Sensitivity of pregnant uterus to oxytocin is higher than that of non-pregnant uterus. High doses of hormone (up to 10 units) cause more frequent and stronger uterine contractions and promote the increase of intrauterine pressure that can result in disorders of blood supply to placenta.

Oxytocin is destroyed when taken orally; therefore, drug is administered intravenously drop-by-drop. The drug effect develops in 0.5–2 minutes. Oxytocin undergoes fast biotransformation in the liver and kidneys. To arrest postpartum uterine hemorrhage, oxytocin may be administered intramuscularly.

Demoxytocin is a synthetic analogue of oxytocin with higher activity. Buccal tablets of the drug are taken sublingually. Desaminooxytocin is used to accelerate postpartum uterine involution and to stimulate lactation.

Pituitrinum contains two hormones of posterior pituitary – oxytocin and vasopressin. Therefore, this drug not only stimulates the uterine contraction, but also increases the blood pressure. The drug is administered subcutaneously or intramuscularly. Therapeutic indications are the same as for oxytocin.

Prostaglandins Preparations

Small amount of prostaglandins is permanently synthesized in the uterus. Prostaglandins dilate the uterine vessels and exert cytoprotective effect due to improving of placental blood supply. Concentration of prostaglandins significantly increases during labor. Prostaglandins E_2 and $F_{2\alpha}$ are used as medications.

Dinoprost (*prostaglandin* $F_{2\alpha}$) inhibits the function of corpus luteum, blocks progesteron synthesis, and increases the level of estrogens. The drug sensitizes myometrium to oxytocin. Dinoprost causes rhythmical contraction, increases the tone of both pregnancy and non-pregnancy uterus, and relaxes uterine neck.

Prostaglandin $F_{2\alpha}$ increases bronchial tone, stimulates cardiac rhithm and force of cardiac contraction, increases gastrointestinal motility, constricts pulmonary vessels, and increases the vascular permeability.

Methyldinoprost is more active and long-acting dinoprost analogue.

Dinoproston (*prostaglandin* E_2) causes the rhythmic uterine contraction and relaxes uterine neck. The drug decreases peripheral vascular resistance, dilated pulmonary vessels and bronchi, increases capillary permeability, stimulates gastrointestinal motility, and inhibits gastric secretion.

Dinoprost and dinoproston cause degeneration of corpus luteum (luteolysis). As partus stimulants, these drugs differ from oxytocin by their ability to relax uterine neck.

Prostaglandins administration can cause excessive uterine contraction with disorders of uterine and placental circulation. Duration of prostaglandins action is longer than that of oxytocin. Most common side effects of prostaglandins include nausea, diarrhea, headache, and elevation of body temperature. Intravenous administration of prostaglandins can cause phlebitis. Due to lot of side effects, prostaglandins are seldom used for stimulation of labor. Drugs may be used for abortions.

Estrogens

Such estrogens as *estron (folliculin)*, *estradiol*, and *synestrol* are commonly used to stimulate labor. These drugs increase oxytocin level by means of inhibition of oxycitonase. Besides, estrogens sensitize oxytocin receptors. Estrogens preparations are administered parenterally.

β-Adrenergic Antagonists

Propranolol (anaprilinum) decreases tocolytic effect of catecholamines, which are released through β_2-adrenergic receptors. To stimulate labor, propranolol is administered intravenously drop-by-drop. The drug is contraindicated in parturient women suffering from heart failure, hypotension, bronchial asthma, and conduction blocks.

Miscellaneous Drugs

The following drugs may be used to stimulate labor: *proserinum, serotonin, pachycarpine, quinine, castor oil, calcium chloride, ascorbic acid,* and *vitamin* B_1.

Proserinum inhibits acetylcholinesterase activity and provides accumulation of acetylcholine in M-cholinergic synapses of uterus that increases the uterine contraction.

Serotonin stimulates the intensivity of mitochondrial respiratory function in myofibrils, influence ATP, actomyosin, and calcium. The drug improves membrane permeability for calcium ions that leads to the increase of uterine contraction.

Serotonin is administered intravenously drop-by-drop.

Pachycarpine is a ganglionic blocker. The drug blocks N_n-cholinergic receptors of mesenteric ganglion and sympathetic ganglions. Besides, pachycarpine stimulates the release of oxytocin by posterior pituitary and sensitizes myometrium to action of estron and oxytocin.

Quinine inhibits oxytocinase and increases oxytocin concentration. It should be noticed that quinine causes bradycardia both in mather and in fetus that restricts its use.

Castor oil increases the cholinergic influence upon the uterus and, therefore, stimulates uterine contraction.

It should be noticed that proserinum, serotonin, pachycarpine, quinine, and castor oil are not used to stimulate labor nowadays.

Such vitamins as *ascorbic acid* and *thiamin* induce labor. Vitamin C stimulates synthesis of estrogens, which stimulate the uterine contraction. Thiamin stimulates synthesis of acetylcholine and inhibits the activity of acetylcholinesterase. These effects result in stimulation of labor.

Drugs Decreasing Uterine Tone and Contractile Activity (Tocolytics)

Stimulation of β_2-adrenergic receptors leads to the decrease of uterine contractile activity and its relaxation. Density of β_2-adrenergic receptors in the uterus depends on periods of pregnancy. The highest density of β_2-adrenergic receptors in the uterus is observed during the last trimester of pregnancy that provides the rest of the uterine muscle and childbearing. Before and during labor the density of β_2-adrenergic receptors decreases that is accompanied by the increase of uterus sencitivity to oxytocin and estrogens.

β_2-Adrenergic agonists are reliable drugs to reduce uterine tone and its contractile activity. These drugs are widely used in obstetric practice. β_2-Adrenergic agonists exert few side effects, are well tolerated by pregnant women, and do not negatively influence upon the fetus and newborn. The following β_2-adrenergic agonists are used as tocolytics: *fenoterol (Partusisten),* *salbutamol (Salbupart),* and *terbutaline (Bricanyl).* These drugs are taken orally or administered intramuscularly and intravenously drop-by-drop. Their maximal tocolytic effect develops in 2 hours after oral intake, in 30 minutes after intramuscular administration, and in 5–10 minutes after intravenous administration. Administration

of β_2-adrenominetics can cause tachycardia (both in mother and fetus), constipations, nausea, anxiety, decrease of diastolic blood pressure, and hyperglycemia.

Therapeutic indicatons for β_2-adrenomimetics are the folliwng:

– to prevent premature labors;

– high tone of the uterine neck at onset of labor;

– excessive fast labor with strong and fast uterine contraction which create a threat of uterine rupture;

– fetus hypoxia caused by labor's abnormalities;

– the need for intrauterine fetal resuscitation;

– performance of intrauterine fetal rotation, especially in case of twins;

– preparation to operation during delivery (cesarean section).

Therapy by *progesterone* or synthetic progestin *turinal* is provided in cases of threat of abortion in early period of pregnancy (under 4 months) and in recurrent abortions owing to insufficient production of progesterone. In these instances, *vitamin E (tocopherol)* is also used.

Magnesium sulfate is an antagonist of calcium. The drug is administered intravenously in dose 5–10 ml of 25% solution to relax uterus. Recently, calcium channel antagonist *nifedipine* is used as tocolytic. Sometimes, general anaesthetic *oxybutyrate sodium (oxybate sodium)* is used to decrease excessive uterine at labor.

Drugs Increasing Uterine Tone and Its Involution in Postpartum Period

Postpartum uterine atony and delayed involution are accompanied by bleeding which can cause the hemorrhagic anemia. The drugs containing ergot alkaloids are most effective agents to eliminate uterine atony: *ergotamine, ergometrine, methylergometrine, ergotal*, and *ergot extract*. Besides, a synthetic drug *cotarnine* is used with this end in view. Oral intake or intramuscular administration of these drugs is accompanied by stable contraction of myometrium that results in mechanical

compression of blood vessels and cessation of hemorrhage. It should be noticed that *oxytocin* exerts similar effect in postpartum period.

There are the following therapeutic indications for the drugs increasing myometrium tone:

– postpartum hemorrhage, uterine atony, delayed involution of uterus, bleeding after manual placental separation;

– dysfunctional uterine bleeding in woman with uterine fibroids;

– hemorrhage associated with inflammation;

Ergot alkaloid ergometrine is also used in the treatment for migraine.

Therapy with ergot alkaloids is accompanied by the following side effects: nausea, vomiting, diarrhea, and headache. Overdose of ergot alkaloids causes the acute poisoning with the following symptoms: motor excitement, convulsions, nausea, vomiting, epigastric pain, tachycardia, and sensation disordes. Long-lasting drug intake leads to chronic poisoning – ergotism which exists in two clinical forms: gangrenous and convulsive. Gangrenous form develops owing to spasm of peripheral vessels and following necrosis of the extremities. Convulsive form is caused by the drug influence upon central nervous system.

Drugs Decreasing the Uterine Neck Tone

The group includes *atropine*, *No-spa*, *dinoprost*, and *dinoprostone*. Theese drugs relax uterine neck and promote labor. Besides, *lidase* is used to reduce cervix rigidity. The drug contains enzyme hyaluronidase which catalyse the degradation of hyaluronic acid.

Table 7 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Dichlothiazidum	Orally 0.025–0.05 g 1–2 times a day	Tablets 0.025 or 0.1 g
Oxodolinum	Orally 0.025–0.1 g once in 2–3 days	Tablets 0.05 g
Triamterenum	Orally 0.05–0.1 g 2 times a day	Capsules 0.05 g

Continuation of the table 7

Drug name (Latin)	Single dose and route of administration	Drug product
Furosemidum	Orally 0.04 g once a day at the morning; intramuscularly or intravenously 0.02 g 1–2 times a day	Tablets 0.04 g; ampoules 2 ml of 1 % solution
Acidum etacrinicum	Orally 0.05–0.1 g 1 time a day or 1 time in 2 days; intravenously 0.05 g once a day	Tablets 0.05 g; ampoules 0.05 g of powder for injection (dissolved before administration)
Spironolactonum	Orally 0.025-0.05 g once a day	Tablets 0.025 g
Mannitum	Intravenously 0.5–1,5 g/kg	Vials 30.0 g of powder for injection (dissolved and used as 10–15 % solution); ampoules 200, 400 or 500 ml of 15 % solution
Ergometrini maleas	Orally 0.000 2–0.000 4 g 2–3 times a day; intramuscularly or intravenously 0.000 1–0.000 2 g 2–3 times a day	Tablets 0.0002 g; ampoules 1 ml of 0.02 % solution
Oxytocinum	Intravenously drop-by-drop 5 IU in 500 ml of 5 % glucose solution; intramuscularly 0.2–2 IU	Ampoules 1 ml (5 IU)
Fenoterolum	Orally 0.005 g 4–6 times a day; intravenously drop-by-drop 0.0005 g in isotonic solution of sodium chloride or glucose	Tablets 0.005 g; ampoules 10 ml of 0.005 % solution

Step 1. Tasks for Self-Control
Diuretic Drugs. Drugs Influencing Myometrium

1. The brain oedema was developed in patient with brain trauma in postoperative period. What drug should be prescribed to this patient?

A. Urea.
B. Furosemide.
C. Amiloride.
D. Dichlothiazidum.
E. Spironolactone.

2. Brain oedema was developed in patient with brain trauma in postoperative period. What drug should be prescribed to this patient?

A. Mannitol.
B. Spironolactone.
C. Amiloride.
D. Dichlothiazidum.
E. Urea.

3. A 46-year-old patient with ciliary arrhythmia had pulmonary oedema. What diuretic is it necessary to use for the treatment of this patient?

A. Dichlothiazidum.
B. Triamterene.
C. Spironolactone.
D. Amiloride.
E. Furocemide.

4. The alternate usage of dichlothiazidum, etacrin acid and lasix did not cause marked diuretic effect in the patient with marked peripheral oedema. The aldosterone level in the blood is increased. Indicate which drug should be prescribed?

A. Spironolactone.
B. Amiloride.
C. Mannitol.
D. Urea.
E. Clopamide.

5. Diuretic drug was prescribed to the patient with hypertension in the course of complex treatment. In a few days blood pressure decreased but signs of hypokalaemia developed. What drug could cause such complications?

A. Triamterene.

B. Clophelinum.

C. Spironolactone.

D. Lasix.

E. Enalapril.

6. Of the following agents, which is best avoided in a patient with a history of chronic congestive heart failure?

A. Spironolactone.

B. Mannitol.

C. Hydrochlorthiazide.

D. Ethacrynic acid.

E. Amiloride.

7. Furosemide inhibits the sodium-potassium dichloride (Na^+, K^+, $2Cl^-$) co-transporters that are located in the:

A. Distal convoluted tubule.

B. Collecting duct.

C. Descending limb of Henle's loop.

D. Proximal tubule.

E. Ascending limb of Henle's loop.

8. Hyperkalemia is a contraindication to the use of which of the following drugs?

A. Hydrochlorothiazide.

B. Etacrynic acid.

C. Spironolactone.

D. Furosemide.

E. Chlorthalidone.

9. A reduction in insulin release from the pancreas may be caused by which of the following diuretics?

A. Amiloride.

B. Triamterene.

C. Spironolactone.
D. Hydrochlorthiazide.
E. Etacrynic acid.

10. A patient with nephrotic diabetes insipidus is best treated with which of the following?

A. Etacrynic acid.
B. Triamterene.
C. Furosemide.
D. Spironolactone.
E. Hydrochlorthiazide.

11. A 50-year-old male with pitting oedema of the ankles develops gynecomastia and erectile dysfunction while being treated with which of the following agents?

A. Amiloride.
B. Furosemide.
C. Spironolactone.
D. Triamterene.
E. Hydrochlorthiazide.

12. From the list of diuretic drugs choose the agent that is most useful for the treatment of acute pulmonary oedema.

A. Triamterene.
B. Hydrochlorthiazide.
C. Furosemide.
D. Spironolactone.
E. Amiloride.

13. From the list of diuretic drugs choose the agent that is most useful for the treatment of acute hypercalcemia.

A. Hydrochlorthiazide.
B. Amiloride.
C. Furosemide.
D. Spironolactone.
E. Triamterene.

14. From the list of diuretic drugs choose the agent that is most useful for the treatment of essential hypertension.

A. Triamterene.
B. Hydrochlorthiazide.

C. Furosemide.

D. Spironolactone.

E. Amiloride.

15. The solution of some drug was introduced to pregnant woman for prevention of premature delivery. This drug is also known as anticonvulsant, hypotensive, cholagogic, and laxative drug. Contraction of uterus and pain stopped, soothing effect occurred. What drug has been prescribed to woman?

A. Salbutamol.

B. Oxytocin.

C. Fenoterol.

D. Magnesium sulfate.

E. Ergometrine maleate.

16. A patient with chronic cardiovascular insufficiency had signs of lungs oedema. What diuretic should be prescribed to the patient for the fast elimination of this condition?

A. Furosemide.

B. Spironactone.

C. Clopamide.

D. Diacarb (acetazolamide).

E. Triamterene.

17. The significant decrease of blood pressure has developed in patient in the result of diuretic overdose. Choose the group of hypertensive drugs which is preferable for using to this patient.

A. N-cholinomimetics.

B. Cardiac glycosides.

C. Analeptics.

D. Plasma substitutes.

E. Adrenomimetics.

18. A patient with pulmonary edema is delivered to resuscitation unit. What drug should be administered to patient for decreasing of blood pressure in small circle of circulation and for decreasing of circulating blood volume?

A. Acetylcysteine.

B. Unithiol.

C. Sulfacyl sodium.

D. Metronidazole.

E. Furosemide.

19. Ascites has developed in patient with cirrhosis. Indicate the drug which should be administered to him for excretion of humor from body.

A. Aminazine.

B. Potassium chloride.

C. Furosemide.

D. Atropine sulfate.

E. Heparin.

20. Identify laxative drug which can be used for reflex increasing of uterus contractions in cases of insufficient labor activity.

A. Sustac.

B. Bisacodyl.

C. Magnesium sulfate.

D. Castor oil.

E. Vaseline.

21. Despite treatment with cardiotonics and thiazide diuretic a patient suffering from chronic cardiac failure still presents with edemata and faces a risk of ascites. What medication should be administered in order to increase the diuretic effect of the above-mentioned drugs?

A. Mannitol.

B. Amiloride.

C. Furosemide.

D. Spironolactone.

E. Clopamide.

DRUGS INFLUENCING HEMOPOIESIS

Drugs influencing hemopoiesis are classified as follows.

I. Drugs which influence erythropoiesis.

1. Drugs stimulating erythropoiesis.

1.1. Drugs which are used to treat hypochromic (iron-deficiency) anemias:

– iron-containing mono-drugs: *ferrous sulfate, ferrous lactate,* and *Ferrum-Lek*;

– iron-containing co-formulated drugs: *Fercoven* (iron and cobalt salts with carbohydrate solution), *Ferroplex* (iron lactate with ascorbic acid), *Ferramid* (complex compound of iron with nicotinamide), *Tardyferon* (iron lactate, ascorbic acid, and mucoprotease), *Haemostimulinum* (contains dry cattle blood, iron lactate, and copper sulfate), etc.;

– cobalt-containing drugs: *Coamidum*;

– recombinant human erythropoietins: *epoetin alfa (Eprex)* and *epoetin beta (Recormon)*.

1.2. Drugs which are used in the treatment for hyperchromic anemias: *cyanocobalamin* and *folic acid*.

2. Drugs inhibiting erythropoiesis: *sodium phosphate labelled by radioactive isotope* ^{32}P.

II. Drugs which influence leukopoiesis.

1. Drugs stimulating leukopoiesis:

– non-specific drugs stimulating nucleic acid synthesis: *sodium nucleinate, pentoxyl, methyluracil,* and *Leucogen*;

– myeloid growth factors: *lenograstim (Granocyte), molgramostim (Leukomax),* and *filgrastim (Neupogen).*

2. Drugs which inhibit leukopoiesis.

2.1. Drugs inhibiting leukocytes in interphase:

– alkylating drugs: *cyclophosphan (cyclophosphamide), thiophosphamide (ThioTEPA),* and *myelosanum*;

– antimetabolites: *methotrexate* and *mercaptopurine*;

– cytotoxic antibiotics: *rubomycin*;

– glucocorticoids: *prednisolone* and *dexamethasone*;

– enzyme agents: *L-asparaginase*;

– cytokines: *interferon α*.

2.2. Drugs which inhibit mitosis of leukocytes:

– cytotoxic drugs of plant origin: *vinblastine* and *vincristine*.

Drugs Influencing Erythropoiesis

Iron ions, cyanocobalamin, and folic acid are primarily necessary for normal erythropoiesis. Their deficiency is accompanied by development of anemia. Erythropoietin stimulates erythropoiesis. This hormone is synthesized by peritubular intersticial renal cells (about 90 %) and in the liver (10 %). Erythropoietin stimulates proliferation and differentiation of erythrocytes.

Drugs Stimulating Erythropoiesis

Drugs which are Used to Treat Hypochromic Anemias

Main cause of hypochromic anemia is insufficient hemoglobin production by bone marrow erythroblasts due to iron deficiency. Iron deficiency most commonly develops owing to iron deficit in food, absorption disorders, hemorrhages, during pregnancy, lactation, etc.

Therefore, iron-containing drugs are the main agents which are used in the treatment for hypochromic anemias. Daily demand of iron for adults is about 0.2 mg/kg (considering that only 10 % taken iron is absorbed from gastrointestinal tract). Distribution of iron in organism is the following: about 70 % of iron (3–4 g) is included in hemoglobin, 10–20 % is deposited in the forms of ferritin and hemosiderin, 10 % is included in muscular protein myoglobin, and about 10 % is in structure of respiratory and other enzymes.

Only ionized iron (better in form of divalent ion) is absorbed in gastrointestinal tract. Hydrochloric acid converts molecular iron to ionized form. Ascorbic acid restores trivalent iron to divalent one. Therefore, hydrochloric acid and ascorbic acid are necessary for normal absorption of iron in gastrointestinal tract. Iron absorption occurs mainly in small intestine by means of active transport. Apoferritin of intestinal mucosa binds with iron ions with formation

of ferritin. After entering blood circulation, iron ions interact with β_1-globulin transferrin which delivers iron to various tissues, including bone marrow, where iron is included in hemoglobin. The excess of iron is deposited in forms of ferritin or hemosiderin. Iron is eliminated from the body through intestine (due to epithelial desquamation and with bile), kidneys, and sweat glands.

At hypochromic anemias, iron-containing drugs are prescribed mainly orally. To prevent contact of iron with mucous membrane of oral cavity, iron-containing drugs are used in form of tablets with special coating or in capsules. It is associated with iron ability to bind with hydrogen sulfide and forms iron sulfide coloring teeth black. Therapy with iron preparations commonly causes constipation due to binding of hydrogen sulfide which is physiological stimulant of intestinal peristalsis.

Iron-containing drugs are taken 1.5 hours prior a meal or 2 hours after a meal.

Recently, co-formulated drugs, containing iron, microelements, and vitamins (ascorbic acid and vitamins of group B) are used in medicine for treatment of hypochromic anemias: *Ferroplex, Sorbifer, Ascofer, Globiron*, etc. *Ferrogradumet* is a representative of co-formulated drugs with prolonged action.

Treatment of hypochromic anemia lasts 3–6 months. First improvement of hemopoiesis is observed in 5–7 days after initiation of therapy. If oral therapy by iron-containing drugs is failing, iron-containing drugs are administered parenterally. Parenteral administration of iron-containing drugs is admitted only for in-patients, because it is commonly accompanied by serious side effects: redness of the face and neck, lower back pain and joint pain, tightness in the chest, tachycardia, nausea, vomiting, allergic reactions, etc. These side effects are eliminated by administration of analgesics and atropine.

Coamidum is a cobalt-containing drug which is used in the treatment for hypochromic anemia. It is complex of cobalt and amide of nicotinic acid. Cobalt stimulates erythropoiesis and promotes

absorption of iron from gastrointestinal tract. Coamidum is administered subcutaneously.

Recently, recombinant human erythropoietins are used in medicine: *epoetin alfa (Eprex, Epogen)* and *epoetin beta (Recormon)*. These drugs are used to treat aplastic anemia, anemias occurring due to chronic renal diseases, rheumatoid arthritis, malignant diseases of bone marrow, AIDS, etc. Recombinant human erythropoietins are administered subcutaneously or intramuscularly 3 times a week. Their side effects are headache, hyperkalemia, arthralgias, etc. Initial therapeutic effect of recombinant human erythropoietins develops in 2 weeks; normalization on hemopoiesis is observed in 8–12 weeks.

Drugs Used to Treat Hyperchromic Anemias

Megaloblastic anemia occurs due to deficiency of vitamin B_{12} (cyanocobalamin). Lack of vitamin B_{12} results in disorders of DNA synthesis and specific pathological changes of erythropoiesis. Erythroblast transforms to hyperchromic megaloblast which converted into megalocyte. Megalocytes are characterized by high RNA/DNA ratio, high iron content, and sharply lowered ability to transport oxygen. Because these cells are oversaturated by hemoglobin, color index is usually more than 1.1–1.3. However, the total hemoglobin in the blood is reduced considerably due to the significant decrease erythrocytes amount. Megaloblastic anemia occurs due to the loss of Castle's intrinsic factor – glycoprotein of gastric mucosa which is essential for absorption of vitamin B_{12}. Deficiency of Castle's intrinsic factor develops at Addison Biermer anemia (primary loss of Castle's intrinsic factor), total gastrectomy, atrophy of mucous membrane of stomach and duodenum, exclusively vegetable diet, and invasion by broad tapeworm. Reducrion of vitamin B_{12} absorption leads to disorders of neucleic acid synthesis. Beside erythropoiesis, peripheral nervous system is also affected at megaloblastic anemia. It is due to reduction of myelin synthesis, which needs cyanocobalamin as a cofactor.

At megaloblastic anemia, *cyanocobalamin* is administered intramuscularly once a day or every other day. Normalization of erythropoiesis, functions of gastrointestinal tract and nervous system is observed in 1–2 month.

Folic acid (vitamin Bc) is essential for synthesis of proteins, nucleic acids, and macroergs. Folic acid deficiency leads to disorders of erythropoiesis with development of macrocytic anemia, at which erythroblast turns into hyperchromic macronormoblast with following transformation into macrocyte.

Folic acid is used to treat drug-induced and alimentary macrocytic anemia, celiac sprue, and anemia of pregnancy. Drug-induced macrocytic anemia is developed owing to therapy with dipheninum, phenobarbital, isoniazid, some hormonal drugs, etc.

It should be noticed that alone use of folic acid in patients with megaloblastic anemia normalizes erythropoiesis but does not reduce pathological changes of nervous system and gastrointestinal tract. Therefore, folic acid is used in the treatment for megaloblastic anemia together with cyanocobalamin.

Folic acid is taken orally. Sometimes, the drug causes allergic reactions.

Herbal Drugs Which Used to Treat Anemias

Herbal drugs, containing a variety of microelements, vitamins, antioxidants, and other bioactive substances stimulating erythropoiesis, are widely used to treat anemias. These drugs increase the body resistance to different unfavarable factors, imrove general well-being, stimulate immunity and hemopoiesis.

The following herbal drugs are used in the treatment for anemia: *European wood strawberry fruits, seeds and fruits of black currant, rowan fruits, rose fruits*, etc.

European wood strawberry fruits contain ascorbic and folic acids, pectin, carbohydrates, salts of iron, cobalt, manganese, calcium, magnesium, phosphorus, etc.

Seeds and fruits of black currant contain ascorbic acid, rutin, thiamine, carotene, pectins, carbohydrates, organic acids, potassium and iron salts, etc.

Rose fruits contain ascorbic acid, rutin, riboflavin, phylloquinone, tocopherol, organic acids, pectins, carbohydrates, flavone glycosides, salts of iron, magnesium, manganese, etc. Rose fruits are used as infusion 1 : 20 or as sirup.

Drugs Inhibiting Erythropoiesis

Drugs inhibiting erythropoiesis are used to treat polycythemia (hyperglobulia). Solution of *sodium phosphate labeled by radioactive isotope* ^{32}P is one of these drugs. Therapy by this drug leads to reduction of number of erythrocytes and platelets. The drug is dosed in millicurie and administered intravenously or taken orally.

Drugs Influencing Leukopoiesis

Drugs Stimulating Leukopoiesis

Various poisons, radioactive radiation, certain medicines, etc. can damage leukopoiesis and provoke leukopenia and agranulocytosis. Drugs stimulating leukopoiesis are classified as follows:

– non-specific drugs stimulating nucleic acid synthesis: *sodium nucleinate, pentoxyl, methyluracil,* and *Leukogen*;

– myeloid growth factors: *lenograstim (Granocyte), molgramostim (Leucomax),* and *filgrastim (Neupogen).*

Sodium nucleinate is sodium sult of nucleic acid which obtained from yeast. The drug is administered intramuscularly or taken orally to stimulate leukopoiesis and immunity.

Pentoxyl is a synthetic agent – pyrimidine derivative. Pentoxyl stimulates leukopoiesis, accelerates wounds healing, and exerts anti-inflammatory effect. The drug is taken orally 3–4 times a day.

Methyluracil is a synthetic agent stimulating synthesis of pyrimidine nucleotides, increasing leukopoiesis, accelerating wound healing, and stimulating immunity (antibody synthesis and interferon

production). Also, the drug exerts anti-inflammatory action. Methyluracil is taken orally and applied topically in ointments. Its therapeutic indications are leukopenia, agranulocytosis, gastroduodenal ulcers, wounds, burns, bone fractures, chronic pancreatitis, etc.

Leucogen is prescribed to treat leukopenia and agranulocytosis. The drug potentiates the effects of other leukopoiesis stimulants. Leukogen is taken orally.

Recently, growth factors regulating leukopoiesis have been approved in medical practice: *molgramostim, lenograstim,* and *filgrastim*.

Human recombinant granulocyte-macrophage colony stimulating factor is obtained by means of genetic engineering. Appropriate drug is called *molgramostim (Leucomax)*. It is glycoprotein stimulating proliferation, differentiation, and activity of granulocytes and monocytes. These cells realize phagocytosis, stimulate immunity, and produce biologically active substances regulating cytokines production. Molgramostim increases the body's resiatnce to bacteria, fungi, and tumors. The drug is administered intravenously at inhibition of leukopoiesis due to cancer chemotherapy, after bone marrow transplantation, at aplastic anemia and AIDS. Side effects of molgramostim are nausea, vomiting, diarrhea, hyperthermia, muscular pain, skin rash, and allergic reactions.

Filgrastim (Neupogen) is a recombinant human granulocyte colony stimulating factor. This glycoprotein stimulates proliferation and differentiation of granulocytic progenitor cells and increases the activity of mature granulocytes. Therapeutic indications for filgrastim are the same as for molgramostim. Filgrastim is administered intravenously or subcutaneously. Side effects are seldom and include arthralgias, allergic reactions, hepatic dysfunction, etc.

Pharmacokinetics and pharmacodynamics of leukopoiesis inhibitors are considered at the chapter "Antitumoral drugs".

Table 8 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Ferri lactas	Orally 1.0 g 3–5 times a day	Capsules 1.0 g
Fercovenum	Intravenously 2–5 ml once a day	Ampoules 5 ml
Coamidum	Subcutaneously 0.01 g once a day	Ampoules 1 ml of 1 % solution
Ferrum Lek	Intramuscularly 2 ml 1–2 times a day; intravenously 2–5 ml 1 time a day	Ampoules 2 (for intramuscular introduction) or 5 ml (for intravenous introduction)
Cyanocobalaminum	Subcutaneously, intramuscularly or intravenously 0.000 1–0.000 5 g 1 time a day	Ampoules 1 ml of 0.003 %, 0.01 %, 0.02 % or 0.05 % solution
Acidum folicum	Orally 0.005 g 1 time a day	Tablets 0.001 g
Penthoxylum	Orally 0.2–0.3 g 3 times a day	Coated tablets 0.2 g
Filgrastimum	Intravenously or subcutaneously 0.000 005 g/1 kg 1 time a day	Vials 0.000 3 g or 0.000 48 g of powder for injections
Cyclophosphanum	Orally, intravenously or intramuscularly 0.2–0.4 g 1 time a day	Coated tablets 0.05 g; ampoules 0.1 g or 0.2 g powder for injection
Chlorbutinum	Orally 0.002–0.01 g 1 time a day	Tablets 0.002 g or 0.005 g
Myelosanum	Orally 0.002–0.006 g 1 time a day	Tablets 0.002 g
Mercaptopurinum	Orally 0.001–0.001 25 g/kg 1 time a day	Tablets 0.05 g
Methotrexatum	Orally, intramuscularly or intravenously 0.03 g 2 times per week or 0.05 g 1 time per 5 days	Coated tablets 0.002 5 g; ampoules 0.005, 0.05 or 0.1 g powder for injection
Vinblastinum (Rosevinum)	Intravenously 0.000 15–0.000 3 g/kg 1 time a week	Ampoules 0.005g or 0.01 g powder for injection

Step 1. Tasks for Self-Control
Drugs Influencing Erythro- and Leucopoesis

1. Methotrexate (structural analogue of the folic acid which is competitive inhibitor of the dihydrofolate reductase) is prescribed for treatment of the malignant tumour. On which level does methotrexate hinder synthesis of the nucleic acid?

A. Transcription.
B. Reparation.
C. Mononucleotide synthesis.
D. Processing.
E. Replication.

2. A nucleophilic attack on deoxyribonucleic acid that causes disruption of base pairing occurs as a result of the administration of:

A. Cyclophosphamide.
B. Methotrexate.
C. Prednisolone.
D. Filgrastim.
E. Mercaptopurine.

3. Which of the following is a chemotherapeutic drug that possesses a mechanism of action involving alkylation?

A. Vincristine.
B. Fercoven.
C. Methotrexate.
D. Myelosan.
E. Pentoxyl.

4. Binding to the enzyme dihydrofolate reductase is the mechanism of action for:

A. Vincristine.
B. Cyclophosphamide.
C. Molgramostim.
D. Sodium phosphate with radioactive isotope of ^{32}P.
E. Methotrexate.

5. Which of the following is considered to be the effective mechanism of action of the vinca alkaloids?

A. Inhibition of purine synthesis.
B. Inhibition of the microtubules function.

C. Inhibition of DNA synthesis.

D. Inhibition of protein synthesis.

E. Damage and prevention of DNA repair.

6. A 34-year-old male with Hodgkin's disease is treated with combined chemotherapy with the use of vinblastine. What is the mechanism of this drug action?

A. Scission of DNA strands.

B. Inhibition of dihydrofolate reductase.

C. Inhibition of enzymes involved in purine metabolism.

D. Inhibiotion of topoisomerase.

E. Prevention of assembly of tubulin dimers onto microtubules.

7. A 45-year-old male on combination therapy for remission-maintenance acute lymphocytic leukemia develops suprapubic pain, dysuria, and haematuria. Evidence of haemorrhage and inflammation is apparent on cystoscopy of the urinary bladder. Which of the following agents most likely caused these findings?

A. Vincristine.

B. Cyclophosphamide.

C. Mercaptopurine.

D. Doxorubicin.

E. Methotrexate.

8. Which vitamin can mask the symptoms of pernicious anaemia by alleviating the anemia but not preventing the neurological damage?

A. Vitamin D.

B. Niacin.

C. Vitamin B_{12}.

D. Folic acid.

E. Vitamin C.

9. Neurotoxicity is rarely dose limiting in cancer chemotherapy. The only antineoplastic agent that has a dose-limiting neurotoxicity is:

A. Methotrexate.

B. Cisplatin.

C. Bleomycin.

D. Vincristine.

E. Doxorubicin.

10. Which class of drugs binds avidly to tubulin and cause arrest of cells in metaphase?

A. Antimetabolites.
B. Vinca alkaloids.
C. Alkylating agents.
D. Antiestrogens.
E. Nitrogen mustards.

11. After the examination of a 40-year-old man the diagnosis of hypochromic anemia was made. What drug should be prescribed for this patient?

A. Fercoven.
B. Cyanocobalamin.
C. Pentoxyl.
D. Heparin.
E. Vikasolum.

12. A pregnant woman's blood analysis revealed megaloblasts and a high colour index. The diagnosis is megaloblastic anemia. What drug should be prescribed to the patient?

A. Cyanocobalamin.
B. Pyridoxine hydrochloride.
C. Nicotinic acid.
D. Ascorbic acid.
E. Coamidum.

DRUGS INFLUENCING BLOOD COAGULATION

Two systems exsist in a body in dynamic equilibrium: one of them promotes blood clotting and another system prevents it. The system promoting blood coagulation include platelets and plastic clotting factors which are contained in them, as well as plasma proteins sinthesized in liver (prothrombin, kappa factor, fibrinogen, etc.). The system preventing blood clotting is presented by proteolytic enzyme fibrinolysin (plasmin), its predecessor profibrinolysin (plasminogen), plasma proteins inhibiting thrombin formation (antithrombin III, etc.), as well as substances which are produced or fixed on the vascular endothelium (prostacyclin, heparin, etc.).

Disequilibrium between these two systems leads to either hemorrhage or thrombosis. Sometimes, combination of both phenomena is occurred and syndrome of disseminated intravascular coagulation develops. All mentioned pathological states require the pharmacological correction.

Drugs influencing blood coagulation are classified as follows.

I. Drugs which are used to prevent and treat thrombosis.

1. Drugs decreasing blood coagulation (anticoagulants):

1.1. Directly acting anticoagulants.

1.2. Indirectly acting anticoagulants.

2. Drugs which activate fibrinolysis (fibrinolytics).

3. Drugs decreasing platelets aggregation (antiaggregants).

II. Drugs which promote blood coagulation (hemostatics).

1. Drugs increasing blood clotting (procoagulants).

2. Drugs inhibiting fibrinolysis (antifibrinolytics).

3. Drugs promoting platelets adhesion and aggregation (proaggregants).

Drugs Used to Prevent and Treat Thrombosis

Drugs Decreasing Blood Coagulation (Anticoagulants)

Blood clotting is regulated system of enzymatic reactions in which lot of coagulation factors are participating. Eventual result of this cascade is formation of thrombin converting soluble fibrinogen to insoluble fibrin. When insoluble fibers of fibrin are occurred, blood corpuscles fixed at them and thromb appears.

According to mechanism of action, drugs decreasing blood coagulation are classified as follows.

1. Directly acting anticoagulants (agents which inactivate clotting factors directly in blood): *heparin, nadroparin (Fraxiparine), enoxaparin (Clexane), dalteparin (Fragmin), tinzaparin (Logiparin), hirudin, lepirudin* and *sodium hydrocitrate*.

2. Indirectly acting anticoagulants (agents which inhibit the synthesis of clotting factors in the liver): *neodicumarinum (ethyl biscoumacetate, Pelentan), Syncumar (acenocoumarol), warfarin,* and *phenindione (Phenylinum).*

Directly Acting Anticoagulants

Heparin is a natural anticoagulant synthesized by mast cells and basophilic leukocytes. Especially high concentration of heparin is contained in a liver and lungs. Heparin is an acidic mucopolysaccharide with molecular weight 15 000–20 000 daltons. Heparin molecules contain residues of sulfuric acid. Due to that, they are charged negatively and exert expressed acidity. Heparin is obtained from lungs and liver of cattle. Activity of obtained heparin is determinated by means of biological standardization, 1 mg of a drug should contain 130 units of heparin.

Negatively charged sites of heparin interact with positively charged amino groups of antithrombin III and activate it. Activated molecules of antithrombin III interact with active centres of serine proteases IIa, IXa, Xa, XIa, XIIa, XIIIa and neutralize them. Besides, antithrombin III suppresses the conversion of prothrombin to thrombin.

Moreover, heparin increases the activity of fibrinolytic system by means of binding with antiplasmin.

Also, heparin inhibits the adhesion and aggregation of platelets because heparin molecules fix on the surface of endotheliocytes and blood cells that creates negative charge of endothelial surface and surface of platelets. Thus, heparin is an anticoagulant with antiaggregatory and fibrinolytic activity. Heparin is active both *in vivo* and *in vitro*.

Besides, heparin exerts antiallergic effect. The drug suppresses cooperation of T- and B-lymphocytes and synthesis of immunoglobulins and activates histaminase.

Heparin increases pulmonary ventilation and coronary blood circulation, inhibits complement system, reduces aldosterone synthesis, activates lipoprotein lipase and decreases blood level of cholesterol and β-lipoproteins.

Heparin is administered intravenously, intramuscularly, subcutaneously, in inhalations, and by electrophoresis. Heparin is also used topically in ointments and gels (e. g., *Lioton*® 1 000). At intravenous administration, its effect develops immediately and lasts

4–6 hours. Effect of intramuscularly administered heparin starts in 15–30 minutes and lasts 6–8 hours. At subcutaneous administration, heparin effect develops in 40–60 minutes and lasts up to 12 hours. Maximum effect of inhaled heparin appears in 18–20 hours and lasts up to 2 weeks.

In urgent cases (e. g., acute myocardial infarction), an average therapeutic dose of intravenously administered heparin is 15 000–20 000 units. In critical cases (e. g., pulmonary artery thromboembolism) heparin's dose is increased up to 40 000–60 000 units with the following intramuscular or subcutaneous its administration (5 000–10 000 units) every 4 hours.

Discontinuation of heparin administration should be gradual because a sudden cessation of therapy can provoke hypercoagulation.

There are following therapeutic indications for heparin:

– thrombosis of coronary vessels at myocardial infarction;

– thromboembolism of pulmonary or cerebral vessels;

– thrombophlebitis;

– prevention of thromboembolism during surgery and in postsurgical period in patients with embolism in anamnesis;

– large scale orthopedic surgery and sugery of heart and vessels;

– prevention of blood clotting in an artificial blood-circulation apparatus;

– thrombophlebitis of superficial veins of lower extremities (commonly in form of ointments and gels);

– diseases with increased risk of thrombosis: atrial fibrillation, endarteritis, acute nephritis);

– bronchial asthma and rheumatism.

High-molecular-weight heparin does not cross through placenta and is not excreted in breast milk. Therefore, this heparin is the drug of choice if to need to prescribe a direct anticoagulant to pregnancy and breastfeeding mothers.

Heparin therapy may be accompanied by the following complications.

1. Common complication of heparin therapy is hemorrhage associated with overdose. This complication is treated by

administration of heparin antagonist – protamine sulfate. The drug is administered intravenously slowly considering that 1 mg protamine neutralizes 85–100 units of heparin. Duration of action of protamine sulfate is 2 hours.

2. Thrombocytopenia which may be of two different types. On 2–4 days after initiation of heparin therapy, moderate thrombocytopenia may develop that is transient and is disappeared during following treatment.

Life-threatening thrombocytopenia develops on 6–12 days of treatment. Its mechanism is associated with synthesis of antibodies (immunoglobulins G and M) which cause platelets aggregation. Owing to this, heparin-induced thrombosis (white clot syndrome) develops that can cause embolia.

3. Dyspeptic disorders.

4. Allergic reactions.

5. Osteoporosis and calcification of soft tissues. This complication develops in long-lasting heparin use and is associated with interaction of calcium with heparin and fatty acids, which are formed due to the increase of activity of lipoprotein lipase and parathormone.

6. Alopecia.

7. Sudden cessation of heparin therapy may provoke rethrombosis. For prevention of rethrombosis, discontinuation of heparin therapy should be gradual and with use of indirect anticoagulants.

Recently, the new group of anticoagulants is introduced in medicine – low-molecular-weight heparins: *nadroparin (Fraxiparine), enoxaparin (Clexane), dalteparin (Fragmin),* and *tinzaparin (Logiparin)*. Molecular weight of these heparins is 2 500–8 000 daltons. These drugs are obtained by method of enzymatic depolymerization of heparin by bacterial heparinase. Low-molecular-weight heparins do not change the time of blood coagulation, because these drugs do not inhibit factor IIa (thrombin). Mechanism of action of low-molecular-weight heparins is associated with the increase of antithrombin III action upon

clotting factor Xa which is essential for transformation of prothrombin into thrombin. Main influence of low-molecular-weight heparins is directed to the decrease of adhesion and aggregation of thrombocytes. Bioavailability of these drugs is three times more than bioavailability of heparin. Duration of these drugs action is longer. Therefore, low-molecular-weight heparins are administered subcutaneously 1–2 times a day. Low-molecular-weight heparins seldom cause hemorrhages and thrombocytopenia. Antagonist of low-molecular weight heparins is protamine sulfate.

Hirudin is a direct anticoagulant, which is contained in salivary glands of leech. It is a polypeptide which consists of 65 amino acid residues. Hirudin inactivates thrombin. *Lepirudin* is short-time acting recombinant analogue of hirudin which is used in medicine. Its half-life is 1.3 hours. The drug is administered intravenously. The agent can cause hemorrhages. There are no antagonists of lepirudin.

Recently, some other derivatives of hirudin are approved in medicine: *bivalirudin* and low-molecular-weight analogoues *melagatran* and *ximelagatran*. Bivalirudin is administered intravenously for anticoagulant therapy during percutaneous transluminal coronary angioplasty. Melagatran is administered subcutaneously to prevent venous thromboembolism in patients undergoing hip or knee elective surgery. Ximelagatran is taken orally. Its indications are similar to melagatran.

Sodium citrate is also a directly acting anticoagulant. The agent interacts with calcium ions which participate in transformation of prothrombin into thrombin. To preserve donor blood, 4–5% sodium citrate solution is used.

Indirectly Acting Anticoagulants

Indirectly acting anticoagulants are synthetic agents inhibiting hepatic biosynthesis of vitamin K-dependent clotting factors. This group includes *neodicumarinum (ethyl biscoumacetate, Pelentan), Syncumar (acenocoumarol), warfarin*, and *phenindione (Phenylinum).*

History of discovery of indirect anticoagulants is associated with severe disease of cattle that was at 1922–1924 in USA and Canada. This disease leaded to death of animals. Due to investigations, it was found that animals were feeded by sweet clover of poor quality. Professor Karl Paul Gerhard Link has separated from clover substance, the administration of which to experimental animals caused same disease. This substance was called dicoumarol. It appeared to be that clover is affected by sertain species of mycelial fungus which transfer coumarin of sweet clover to dicoumarol. On the base of this investigations, prof. Link has suggested to use dicoumarol in the treatment for diseases which are accompanied by increased blood coagulation. Presently, dicoumarol is not practically used owing to high its toxicity.

Neodicumarinum (ethyl biscoumacetate, Pelentan) is analogue of dicoumarol with less toxicity. Its chemical structure is similar to molecular structure of vitamin K that that is the base for structural antagonism between neodicumarinum and vitamin K. Mechanism of action of neodicumarinum is associated with inhibition of enzyme epoxide reductase catalyzing transformation of vitamin K epoxide form into the hydroquinone form. Hydroquinone form of vitamin K participates in the synthesis of factor II (prothrombin), factor VII (proconvertin), factor IX (antihemophilic globulin B or Christmas factor), and factor X (Stuart–Prower factor) which are essencial for blood coagulation. Because neodicumarinum inhibits hepatic synthesis of clotting factors, the agent is active only *in vivo*.

Besides, neodicumarinum inhibits the activity of the factor supporting the elastisity of vascular wall. Therefore, long-lasting intake of neodicumarinum increases the fragility and permeability of capillaries.

Neodicumarinum is taken orally 3–4 times a day. The drug is characterized by high degree of gastrointestinal absorption. Anticoagulant effect develops in 2–3 hours and reaches the maximum in 12–24 hours. Latent period of action of indirect anticoagulant is determined by the duration of existence of

previously synthesized clotting factors in the blood. After discontinuation of drug intake, anticoagulative effect lasts 1.5–2 days. At long-lasting therapy, the drug accumulates in the body. It should be noticed that neodicumarinum penetrate through placenta easily.

Therapeutic indications for neodicumarinum are the follows:

1) prevention and treatment of venous thrombosis, thrombophlebitis, myocardial infarction, and ischemic stroke;

2) prevention of thrombosis in postoperative period;

3) prevention of thrombosis and thromboembolia in patients with rheumatic heart damages;

4) prevention of thrombosis after angioplasty, prosthetic heart valves;

5) Prevention of thrombosis after discontinuation of therapy by directly acting anticoagulants.

There are following side effects of neodicumarinum therapy:

1) hemorrhages due to excessive inhibition of blood clotting and increased vascular permeability. In this setting, it is necessary to discontinue neodicumarinum intake and immidiatly administre vitamin K or vicasolum (menadione), vitamins C and P. Blood transfusion is also possible;

2) coumarin-induced necrosis of soft tissues (buttocks, breasts, cheeks, etc.) due to thrombosis of capillaries and small venules. This complication appears at 4–10 days after initiation of drug intake. Coumarin-induced thrombosis more frequently develops in women.

Coumarin-induced necrosis is associated with low level of protein C – a serine protease with anticoagulant and fibrinolytic activity. After initiation of therapy by indirectly acting anticoagulants, the level of protein C is decreased more rapidly than the levels of clotting factors IX, X and II. Therefore, when indirect anticoagulant is given to a patient with low initial level of protein C, a transient hypercoagulable state develops that leads to local thrombosis;

3) dyspepsia;

4) allergic reactions;

5) toxic damage of the liver and kidneys;

6) drug intake by pregnant woman can provoke malformations of the skeleton on the first part of pregnancy and hemorrhage in fetus on late pregnancy;

7) sudden stop of neodicumarinum intake provokes thrombosis.

Mechanisms of action, effects, and indications for use of *warfarin*, *Syncumar*, and *phenindione* are similar to neodicumarinum. Main difference of these drugs is a longer latent period (anticoagulant effect develops in 24–72 hours) and longer duration of action – up to 2–4 days.

Antagonists of indirectly acting anticoagulants are *vitamin K* and its synthetic analogue – *vicasolum*.

Drugs Activating Fibrinolysis (Fibrinolytic Drugs)

Fibrinolytic system prevents intravascular coagulation, restricts clot propagation, and repairs vascular patency after cessation of hemorrhage. Treatment of patients with fibrinolytic drugs is not a substitute for the anticoagulant drugs. Because the purpose of thrombolytic therapy is a rapid lysis of already formed clots, while the aim of anticoagulant therapy is a prevention of the new clotting formation.

Fibrinolysis is initiated due to the transformation of profibrinolysin (plasminogen) into fibrinolysin (plasmin) under influence of plasminogen activators (tissue plasminogen activator, urokinase). Plasmin is a proteolytic enzyme which normally does not exist in blood. Fibrinolysin catalyzes the degradation of fibrin.

Fibrinolytic drugs are devided into 2 groups.

1. Directly acting fibrinolytics: *fibrinolysin (plasmin)*.

2. Indirectly acting fibrinolytics: *streptokinase, streptodecase, anistreplase, urokinase,* and *alteplase (Actilyse)*.

Fibrinolysin (plasmin) is a proteolytic enzyme which is appiared due to activation of profibrinolysin by plasminogen activators. Fibrinolysin causes only superficial lysis of thrombus (predominantly in veins) because it is quickly neutralized by antiplasmin. Fibrinolysin is active both *in vivo* and *in vitro*. The drug

is administered intravenoulsy drop-by-drop. Prior administration, powder for injection is dissolved in sterile isotonic sodium chloride solution or sterile isotonic glucose solution at the ratio of 100–160 units of fibrinolysin per 1 ml of solution. Also, heparin is added to this solution at the ratio 1 units of heparin per 2 units of fibrinolysin. Therapy with fibrinolysin lasts 10–14 days.

There are the following therapeutic indications for fibrinolysin: thrombosis of peripheral arteries, myocardial infarction, ischemic stroke, and thrombosis of peripheral veins. It should be noticed, that in case of arterial trombosis, fibrinolysin is effective during the first day (especially initial 6 hours after thrombosis); while, in case of venous thrombosis, the drug is effective during 5–7 days.

Hemorrhages is a common complication of fibrinolysin therapy. In this case, aminocaproic acid, plasma, or donated blood are administered. Because fibrinolysin is the drug of peptide origin, its administration may provoke allergic reactions.

Streptokinase is an enzymatic agent which is obtained from culture of β-hemolytic streptococcus. It is fibrinolytic drug with indirect action. Streptokinase interacts with plasminogen with formation of active complex which converts molecules of plasminogen into plasmin. Unlike fibrinolysin, streptokinase penetrates inside thrombus where it activates fibrinolysis. The drug is administered intravenously or intra-arterially drop-by-drop during 16–18 hours. Onset of action occurs in 30–60 minutes. The course of treatment lasts 4–6 days.

Therapeutic indications for streptokinase are follows:

1) embolism of pulmonary artery and its branches;
2) acute thrombosis and ambolism of peripheral arteries;
3) acute thrombosis of superficial and deep veins;
4) acute myocardial infarction (during initial 8 hours);
5) acute thrombosis of retinal vessels.

Its side effects include hemorrhages, hemolysis, nephrotoxicity, and allergic reactions. It should be noticed that allergic reactions can occur even at first administration of streptokinase because antibodies to streptococci are commonly present in human body.

Streptodecase is a long-acting preparation containing streptokinase applied on water-soluble polysaccharide matrix. Duration of streptodecase action is 48–72 hours. Drug is administered intravenously.

Recently, another drug containing strepkinase was approved – *anistreplase (Eminase).* It is complex of streptokinase with modified plasminogen. The drug is administered intravenously in coronary thrombosis. Elimination half-life of anistreplase is 70–120 minutes. Its side effects are hemorrhages, allergic reactions, bradycardia, transient hypotension, etc.

Urokinase is a plasminogen activator which obtained by means of gene engineering. Its fibrinolytic effect develops faster than those of streptokinase. Drug is administered intravenously in acute arterial and venous thrombosis of different localization. Urokinase does not exert marked antigenic properties; therefore, its repeated administration causes allergic reactions seldom.

Alteplase (*Actilyse*) is tissue-type plasminogen activator obtained by means of gene engineering. Alteplase exerts high affinity to fibrin of thromb. Therefore, alteplase causes fibrin-selective activation of plasminogen. The drug causes insignificant activation of plasminogen in plasma. Alteplase is administered intravenously or intra-arterialy. Its plasma half-life is 5 minutes. Fibrinolytic efficacy of alteplase is higher than the eficacy of streptokinase. Alteplase is administered intravenously or intra-arterially. Alteplase does not exert antigenic properties. Its possible side effect is hemorrhage.

Recently, *tenecteplase* (*Metalyse*) was approved in medical practice. The drug is a recombinant genetically modified activator of tissue plasminogen. Its plasma half-life is about 20–25 minutes. The drug is administered intravenously in the treatment for acute myocardial infarction. Its most common side effect is hemorrhage.

Drugs Inhibiting Thrombocyte Aggregation (Antiaggregants)

In significant degree, platelet aggregation depends on ratio of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2). ADP released from the platelet granules activate phospholipase A_2. In platelets, phospholipase A_2, cyclooxygenase 1, and thromboxane synthetase consequentially convert arachidonic acid into cyclic endoperoxides and TXA_2. Thromboxane A_2 promotes adhesion and aggregation of thrombocytes. In endotheliocytes, prostacyclin synthetase converts cyclic endoperoxides into prostacyclin which decreases platelets aggregation and adhesion.

There are other endogenous substances promoting platelet aggregation: serotonin, epinephrine, thrombin, collagen of vascular wall, prostaglandin E_2, etc. Endogenous substances with opposite function are prostaglandin E_1, heparin, cAMP, adenosine, NO, etc. If the equilibrium TXA_2 / PGI_2 is broken for the benefit of TXA_2, the platelet aggregation is increased that can provoke myocardial infarction, ischemic stroke, etc.

Antiaggregants are drugs which decrease platelets aggregation and adhesion. Their clinical use is effective in regard to prevent thrombosis, because reversible aggregation of thrombocytes critically fastly turns out irreversible with formation of strong links between thrombocytes.

According to mechanism of action, antiaggregants are classified as follows:

1) agents inhibiting activity of thromboxane system: *acetylsalicylic acid (aspirin), dasoxiben,* and *ridogrel.*

2) drugs which increase the activity of prostacyclin system: *epoprostenol (prostacyclin);*

3) drugs inhibiting fibrin binding with thrombocyte receptors: *ticlopidine (Ticlid), clopidogrel (Plavix),* and *abciximab (ReoPro);*

4) drugs with different mechanism of action: *dipyridamole, pentoxifylline (Trental).*

Drugs Inhibiting Activity of Thromboxane System

Acetylsalicylic acid (*aspirin*) exerts dose-dependent effects. To the extent that drug concentration in the blood is increased, the following effects appear: antiaggregant, antipyretic, analgesic, and anti-inflammatory.

Acetylsalicylic acid irreversibly inhibits cyclooxygenase by acetylation of it. This process develops both in platelets, preventing the formation of TXA_2, and in endothelial cells, inhibiting the synthesis of PGI_2. But endothelial cells can synthesize a new cyclooxygenase while platelets can not, because platelets have not nucleus. Therefore, ratio TXA_2 / PGI_2 changes in favor of prostacyclin. The aim of therapy with acetylsalicylic acid is the selective inhibition of TXA_2 synthesis in the platelets that leads to the decrease of platelet aggregation. It is achieved by drug intake in dose 50–125 mg per day. Activity of cyclooxygenace in endotheliocytes is resotered in several hours. Whereas activity of thrombocytar cyclooxygenase is restored only due to formation of new thrombocytes. It should be noticed that duration of thrombocyte life is 7–10 days.

Nitro-aspirin is aspirin derivative containing a nitro moiety. In the body, the drug releases nitric oxide (NO). Nitro-aspirin both decreases vascular tone and inhibits platelet aggregation.

Dazoxiben is a selective inhibitor of thromboxane synthase. As a rule, dasoxiben is used in combination with acetylsalicylic acid.

Drugs Increasing the Activity of Prostacyclin System

Prostacyclin (epoprostenol) dilates blood vessels and inhibits platelets aggregation. Because the drug has a very short duration of action, epoprostenol is administered intra-arterially drop-by-drop to treat vascular diseases of lower extremities. Epoprostenol improves blood circulation in skeletal muscules, decreases ischaemic pain, and promotes the healing of trophic ulcers. The drug is also used to prevent thrombocyte adhesion to dialysis membrane at hemodialysis and hemosorption, and in apparatus of extracorporeal circulation.

Drugs Inhibiting Fibrin Binding with Thrombocyte Receptors

Abciximab (ReoPro) irreversibly blocks platelet glycoprotein receptors (GP IIb/IIIa) and prevents fibrinogen binding with them that leads to inhibition of platelet aggregation. Besides, the drug exerts anticoagulant activity. Abciximab is administered intravenously to treat myocardial infarction, severe angina pectoris, and to prevent blood coagulation during angioplasty. Its duration of action is about 24 hours. Most common side effect of abciximab is hemorrhages.

Eptifibatide and *tirofiban* exerts identical mechanism of action to abciximab. Their duration of action is less (2–8 hours).

Ticlopidine (*Ticlid*) inhibits platelet aggregation by means of blockage of platelet P_2-purinergic receptors activated by ADP. Due to this, the drug prevents ADP-induced binding of fibrinogen with glycoprotein receptors of thrombocytes. Its antiaggregative effect is higher than those of aspirin. Antiaggregative effect develops gradually within 3–5 days. Ticlopidine is taken orally 2 times a day while eating. Its therapeutic indications are myocardial infarction, unstable angina pectoris, ischemic stroke, and angioplasty. The drug is prescribed to patients who no tolerate aspirin. Side effects of ticlopidine are gastrointestinal disorders, leukopenia, agranulocytosis, elevation of level of atherogenic lipoproteins, and allergic reactions.

Clopidogrel (*Plavix*) exerts identical mechanism of action to ticlopidine. The drug is taken orally once a day. The drug produces fewer side effects than ticlopidine. Bone marrow toxicity is uncharacteristic of clopidogrel.

Drugs with Different Mechanism of Action

Dipyridamole is a coronary vasodilator with antiaggregant activity. The drug inhibits phosphodiesterase that leads to elevation of cyclic adenosine monophosphate (cAMP) concentration in platelets. Besides, dipyridamole blocks adenosine deaminase and prevents destruction of adenosine which inhibits the platelets

aggregation and dilates vessels. Dipyridamole is also used with aspirin in co-formulated preparation *Aggrenox*. Side effects of dipyridamole include headache, dispepsy, hypotension, allergic reactions, and steal syndrome.

Pentoxifylline (*Trental, Dartelin*) is a xanthine derivative. The drug inhibits phosphodiesterase and promotes accumulation of cAMP in platelets that leads to the decrease of platelet aggregation. Besides, pentoxifylline blocks P_2-purinergic receptors, decreases thromboxane A_2 synthesis, and increases prostacyclin synthesis. The drug activates glycolysis in erythrocytes that leads to accumulation of ATP and diphosphoglycerate. Owing to this, the elasticity of erythrocytes increased that improves capillary circulation. Also, pentoxifylline increases the release of plasminogen activator, reduces the level of fibrinogen, and decreases blood viscosity. The drug exerts moderate vasodilative activity. Under the influence of pentoxifylline, blood rheology is improved. Marked therapeutic effect of pentoxifylline is observed in 2–4 weeks after initiation of therapy. Pentoxifylline is used to treat Raynaud's disease, diabetic angiopathy, disorders of cerebral and coronary circulation, and shock. Its side effects are appetite loss, diarrhea, nausea, dizziness, hypotension, and facial flushing.

Sulfinpyrazone (Anturan) is antigout drug. But also, the drug inhibits adhesion and aggregation of thrombocytes. Its antiaggregant activity is low.

Drugs Promoting Blood Coagulation (Hemostatics)

Drugs, which promote hemostasis, are used to prevent and treat acute and chronic hemorrhages. Disorders of blood coagulation develop due to genetically determinated deficiency of clotting factors (haemophilia), sharp fibrinolysis activation, inhibition of adhesion and aggregation of thrombocytes, surgery (especially on the lungs and pelvic organs), hepatic diseases, protein starvation, shock, radiation sickness, intoxications, etc. To cessate hemorrhages, the following groups of drugs are used: drugs increasing blood clotting

(procoagulants), antifibrinolytics, and drugs promoting platelets agregation.

Drugs Increasing Blood Clotting (Procoagulants)

Procoagulants are classified as follows.

1. Drugs for topical application: *thrombin*, *hemostatic sponge*, and *beriplast*.

2. Drugs for systemic action: *vicasolum*, *phytomenadione*, *fibrinogen*, *calcium chloride*, *calcium gluconate*, *gelatin*, *etamsylate*, *VIII* and *IX clotting factors*.

Thrombin is an active key factor of blood coagulation which converts fibrinogen to fibrin. The drug is obtained from donated blood. This drug is applied topically at surgery on parenchymatous organs (most commonly on the liver), at hemorrhages from osteal tissues, and gingiva. The parenteral introduction of thrombin is inadmissible, because the drug rapidly causes the generalized thrombosis. Sometimes, thrombin is taken orally at gastral hemorrhages or inhaled at lessions of respiratory tract.

Hemostatic sponge is obtained from plasma. The drug contains also calcium chloride and aminocaproic acid. Hemostatic spongle is used only topically to arrest capillary bleeding.

Vitamin K exists in two forms: K_1 *(phylloquinone)* and K_2 *(menaquinone)*. Phylloquinone is contained in green parts of plants. Menaquinone is synthesized by intestinal bacterial flora and is contained in animal liver. Bile acids are essential for intestinal absorption of vitamin K; therefore, this process may significantly slow down at hepatic diseases.

Vitamin K participates in hepatic synthesis of K-dependent factors of blood coagulation: II (prothrombin), VII (proconvertin), IX (Christmas factor), and X (Stuart-Prower factor).

Phytomenadione (phytonadione) is synthetic preparation with identical activity to natural phylloquinone. The drug is taken orally 30 minutes before a meal or administered parenterally – subcutaneously, intramuscularly, or intravenously.

Vicasolum (menadione sodium bisulfite) is another synthetic analogue of vitamin K. Vicasolum is taken orally or administered intramuscularly 2–3 times a day. In the liver, vicasolum transforms into vitamin K_1 and K_2. The response to vicasolum drugs is slow and requires about 24 hours.

Besides procoagulant, vitamin K also exerts antihypoxic activity and participates in hydrogen transport in respiratory chain. Therefore, vitamin K is essential for mitochondrial ATP synthesis.

Vitamin K deficiency is commonly observed against the background of the parenteral feeding, antibiotic therapy, and due to overdose of indirect anticoagulants. Also, vitamin K deficiency is observed in premature newborns.

Clinical applications for preparations of vitamin K are the follows:

– prevention and treatment of hemorrhages in pre- and aftersurgical periods;

– hemorrhages at ulcer disease and radiation sickness;

– uterine bleeding;

– early and later forms of hemorrhagic disease of newborns (early hemorrhagic diseases developed during 1st day of life, later – in 1 month);

– hypoprothrombinemia;

– parenchymatous bleeding, etc.

Fibrinogen is obtained from donated blood. The drug is administered intravenously drop-by-drop through the system with special filter during 2–4 hours 1 time a day under control of blood coagulation. The drug is used to cessate hemorrhages appeared due to hypofibrinogenemia: some hepatic diseases, overdosage of fibrinolitics or indirects anticoagulants, and in protein starvation, etc. Also, fibrinogen is preventively used before surgery on organs riching on tissue activators of fibrinolysis (lung, pancreas, prostates, and thyroid glands). Fibrinogen is used in obstetrics at placental abruption, cesarean section, and artificial delivery.

Calcium-containing drugs (*calcium chloride* and *calcium gluconate*) stimulate the formation of thromboplastin, conversion

of prothrombin to thrombin, and fibrin polimerization. Besides, calcium ions decrease vascular permeability. Calcium salts are used at internal bleeding appeared due to thrombocytopenia and increased vascular permeability. Also, calcium-containing drugs are administered to recipients at transfusion of citrated blood.

Gelatin contains high quantity of calcium ions, and due to that, increases the blood coagulation. Also, gelatin increases blood viscosity and thromboplastin release. 10 % gelatin solution is administered intravenously.

Etamsylate stimulates the formation of thromboplastin. Also, the drug inhibits hyaluronidase that results in stabilization of vascular wall. Etamsylate is used to prevent and interrupt capillary bleeding at diabetic angiopathy and various surgery. The drug is taken orally or administered parenterally.

VIII and *IX clotting factors* are obtained from donated blood and stored frozen. These drugs are used at hemorrhages due to deficiency of corresponding clotting factors. Deficiency of these factors is genetically determinated. Deficiency of VIII factor (anti-hemophilic factor) causes haemophilia A; while deficiency of IX factor leads to haemophilia B (Christmas disease). In both cases, blood loses completely the ability to coagulate. Hemorrhages appeared at these diseases require administration of corresponding clotting factors during 3–10 days. A cost of these drugs is very high. Pharmaceutical industry produces coformulated drugs (*Autoplex, Feiba*) which contain both mentioned active clotting factors and are effective even antibodies or inhibitors of these factors are present in blood of patient.

Drugs Inhibiting Fibrinolysis (Antifibrinolytic Drugs)

Increased fibrinolytic activity is due to overdose of fibrinolytic drugs, sepsis, severe traumas of internal organs, etc. Hemorrhages appeared owing to increased fibrinolytic activity are poorly treated by procoagulants and require an administration of antifibrinolytic drugs, fibrinogen, or plasma.

Antifibrinolytic drugs are *Contrical, Trasylol, Gordox* (*aprotinin* is an active substance of these drugs), *aminocaproic acid (Amicar), aminomethylbenzoic acid (Pamba), tranexamic acid (Cyklokapron).*

Aminocaproic acid is a synthetic agent – lysine derivative. The drug interacts with profibrinolysin activator and inhibits it that prevents the transformation of profibrinolysin into fibrinolysin. Besides, aminocaproic acid interacts with active centres of profibrinolysin and fibrinolysin and inhibits their activity. The drug is taken orally or administered intravenously drop-by-drop. Its duration of action is 6 hours; therefore, the drug is taken 4 times a day. Side effects of aminocaproic acid are allergic reactions and dispeptic disorders. Intravenous administration of aminocaproic acid is accompanied by hypotension, thrombosis, embolism, disorders of color vision, etc.

Aminomethylbenzoic acid (Pamba) is a synthetic drug with activity which is 3–7 times more than those of aminocaproic acid. The drug is taken orally and administered intravenously. Its duration of action is 3–8 hours.

Tranexamic acid (Cyklokapron) exerts higher antifibrinolytic activity than aminocaproic acid. The drug is taken orally or administered intravenously. At intravenous administration, its half-life is 2 hours.

Aprotinin is an active substance of such drugs as *Contrical, Trasylol, Gordox*, etc. This protease inhibitor directly inhibits fibrinolysin, trypsin, chemotrypsin, kallikrein and other proteolytic enzymes. Inhibition of trypsin and chemotrypsin provides therapeutic effect of aprotinin at acute pancreatitis. Blockage of kallikrein and reduction of level of bradykinin and kallidin decrease bronchospastic and allergic reactions in the body.

Gordox is obtained from animal pancreas, Contrical – from animal lungs, and Trasylol – from parotid glands. These drugs are administered intravenously slowly or drop-by-drop. The drugs are completely inactivated in the body in 2–4 hours after their administration.

There are the following therapeutic indications for antifibrinolytics:

– overdose of fibrinolytics;

– surgery and traumas of organs, which are rich by proteolytic enzymes (lungs, uterus, pancreas, prostate, etc.);

– hemorrhagic insult;

– placental abruption, intrauterine death of fetus;

– acute pancreatitis;

– renal ischemia;

– staphylococcal pneumonia with phenomena of destruction;

– pulmonary haemorrhages at tuberculosis;

– gastric hemorrhages at ulcer disease, etc.

Drugs Promoting Platelets Aggregation

This group includes such drugs as *serotonin, etamsylate (Dicynone), carbazochrome (Adroxon), calcium gluconate,* and *calcium chloride*.

Serotonin is an endogenous amine synthesized from tryptophan in body tissues. It stimulates S_1- and S_2-serotonergic receptors on the platelet surface that promotes the platelet aggregation. Besides, serotonin causes vasospasm and increases vascular permeability. The drug is administered intravenously or intramuscularly at hemorrhages, hypo- and aplastic anemias. Adverse effects are bronchospasm, intestinal spasms, vascular spasm, etc.

Adroxon (carbazochrome) is epinephrine derivative unable to stimulate the adrenoceptors of smooth muscles and heart. Due to excitation of α-adrenoceptors of platelets, the drug activates phospholipase C that leads to release of substances stimulating platelet aggregation. Adroxon is taken orally, administered subcutaneously or intramuscularly, and applied topically.

Calcium chloride and *calcium gluconate* increase platelet aggregation, activate thrombin formation, and decrease vascular permeability. Calcium gluconate is administered intramuscularly, intravenously or taken orally before a meal. Calcium chloride is intended for intravenous administration or taken orally after a meal. The frequency of administration for both drugs is 3–4 times a day.

These drugs are used to treat hypocalcemia, thrombocytopenia, angiasthenia, hemorrhages at gastroduodenal ulcers, pulmonary diseases, uterine hemorrhages, etc.

Etamsylate (Dicynone) is one of the most effective proaggregants. The drug blocks prostacyclin effects that increases platelet aggregation. Besides, etamsylate promotes polymerization of hyaluronic acid that increases a density of basal membrane of capillary wall. Etamsylate is used in the treatment for parenchymatous and capillary hemorrhages and at thrombocytopenia. The drug is administered intravenously and intramuscularly or taken orally 3–4 times a day.

It should be noticed that besides mentioned above drugs, glucocorticoids, ascorbic acid, and rutin also decrease vascular permeability.

Table 9 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Acidum acetylsalicylicum	Orally 0.075–0.325 g once a day	Tablets 0.075 or 0.325 g
Dipyridamolum	Orally 0.025–0.05 g 3 times a day	Tablets 0.025 or 0.075 g
Heparinum	Intravenously 5 000–20 000 IU 4 times a day	Vials 5 ml (1 ml – 5 000, 10 000, or 20 000 IU)
Calcii chloridum	Intravenously slowly 0.5–1.0 g 1–2 times a day	Ampoules 5 or 10 ml of 10% solution
Neodicumarinum	Orally 0.05–0.1 g 3 times a day	Tablets 0.05 or 0.1 g
Syncumarum	Orally 0.001–0.006 g 1–2 times a day	Tablets 0.002 or 0.004 g
Streptokinasum	Intravenously drop-by-drop 250 000–500 000 IU (250 000 IU is dissolved in 50 ml sterile isotonic sodium chloride solution)	Ampoules 250 000 or 500 000 IU of powder for injection
Acidum aminocapronicum	Orally 2–3 g 4 times a day; intravenously drop-by-drop 5.0 g once a day	Powders for internal use; vials 100 ml of 5% solution

Continuation of the table 9

Drug name (Latin)	Single dose and route of administration	Drug product
Contricalum	Intravenously drop-by-drop 10 000–50 000 IU 4–6 times a day	Vials containing 10 000, 30 000 or 50 000 IU of powder for injection
Fibrinogenum	Intravenously drop-by-drop 1.0–2.0 g (1g is dissoled in 250 ml of water for injections)	Vials containing 1.0 or 2.0 g of powder for injection
Vikasolum	Orally 0.015 g 2–3 times a day; intramuscularly 0.01 g 1 time a day	Tablets 0.015 g; ampoules 1ml of 1% solution

Step 1. Tasks for Self-Control
Drugs Influencing Blood Coagulation

1. A patient with thrombophlebitis is administered the complex therapy, which influences different stages of clot-forming. Which of the given substances contributes to the restoration of the vascular permeability?

A. Acetylsalicylic acid.
B. Fibrinolysin.
C. Heparin.
D. Neodicumarinum.
E. Dipyridamole.

2. Some drug had been prescribed to the patient with thromboembolism of lower extremities veins. In 2 days haemorrhages appeared on his skin. What drug was prescribed to the patient?

A. Heparin.
B. Dipyrodamole.
C. Acetylsalicylic acid.
D. Neodicumarinum.
E. Phenylinum.

3. An 8-year-old child is being prescribed for tonsillectomy. The analysis of blood has shown that the time of blood coagulation is

increased (up to 7 minutes). What drug should be included (5 days before the operation) into the complex of therapeutic agents of the preparatory period first of all?

A. Etamsylate.

B. Sodium chloride.

C. Aminocaproic acid.

D. Fibrinogen.

E. Vicasolum.

4. A doctor recommended to patient, who had an acute myocardial infarction, to take acetylsalicylic acid in the dose 0.25 g once per 2–3 days during 3–4 months. What effect did the doctor count on?

A. Vasodilative.

B. Antiaggregant.

C. Antipyretic.

D. Analgesic.

E. Anti-inflammatory.

5. Acetylsalicylic acid (75 mg, daily) is prescribed to the patient, who had myocardial infarction. What is the purpose of this prescription?

A. Reduction of body temperature.

B. Reduction of inflammation.

C. Reduction of pain.

D. Reduction of thrombocytes aggregation.

E. Dilation of coronary vessels.

6. Vicasolum is prescribed to patient during several days before planned surgery concerning an ulcer of stomach. What is the mechanism of vicasolum action?

A. Drug binds the calcium ions.

B. Drug decreases vessels permeability.

C. Drug oppresses fibrinolysis.

D. Drug oppresses aggregation of thrombocytes.

E. Drug increases blood clotting in the result of increasing of prothrombin synthesis.

7. A patient with myocardial infarction is delivered to resuscitation unit. What drug should be administered to the patient for prevention of thrombus formation?

A. Heparin.

B. Chingaminum.

C. Thyroxine.

D. Biseptol 480.

E. Dimedrol.

8. Patient with angina pectoris is treated with acetylsalicylic acid in daily dose 100 mg daily. What is the aim of therapy with acetylsalicylic acid in this case?

A. Decrease of cholesterol level.

B. Inhibition of blood clotting.

C. Dilation of coronary vessels.

D. Decrease of prothrombin level.

E. Inhibition of platelet aggregation.

DRUGS INFLUENCING METABOLISM

VITAMINS

This group includes drugs containing vitamins of natural and synthetic origin which are essencial for body metabolism.

Vitamins are used to treat and prevent hypo- and avitaminosis and to treat certain pathological states by means of targeted metabolism regulation.

Vitamin deficiency (hypo- and avitaminosis) develops due to their insufficient intake, disorders of their absorption in some gastrointestinal diseases, or in case of increased organism demand in vitamins (pregnancy, fever, thyrotoxicosis, etc.).

Vitamins are classified as follows.

1. Water-soluble vitamins: *ascorbic acid (vitamin C), rutin (vitamin P), thiamine (vitamin B_1), riboflavin (vitamin B_2), panthotenic acid (vitamin B_5), pyridoxine (vitamin B_6), cyanocobalamin (vitamin B_{12}), folic acid (vitamin B_c), and nicotinic acid (vitamin PP).*

2. Lipid-soloble vitamins: *retinol (vitamin A), tocopherol (vitamin E), ergocalciferol (vitamin D), and naphthoquinones (phylloquinone – vitamin K_1; menaquinone – vitamin K_2).*

Drugs of Water-Soluble Vitamins

Thiamine (Vitamin B_1)

Thiamine is found in the bran of cereal grain, rice, peas, yeast, and other products of plant and animal origin.

Thiamine bromide and *thiamine chloride* are preparations of vitamin B_1 which dosed orally or parenterally. In a body, thiamine undergoes phosphorylation with formation of thiamine monophosphate and thiamine diphosphate. Thiamine diphosphate is most effective and manufactured by pharmaceutical industry with name Cocarboxylase. Thiamine diphosphate participates in decarboxylation of pyruvic acid and α-ketoglutaric acid. Pyruvic acid is essential for formation of acetate which is used for synthesis of acetyl-CoA, acetylcholine, steroid hormones, and fatty acids.

α-Ketoglutaric acid is involved in citric acid cycle (Krebs cycle) and is essential for synthesis of ATP.

Also, thiamine diphosphate is coenzyme of transketolase. It is key enzyme of pentose phosphate pathway, which is essential for synthesis of nicotinamide nucleotides, fatty acids, nucleic acids, proteins, etc.

Thereby, vitamin B_1 participates in regulation of carbohydrate, energy, peptide, and other types of body metabolism. Thiamine diphosphate eliminates metabolic acidosis.

Thiamine dilates coronary vessels and improves blood supply of myocardium. The drug stimulates cardiac contraction and improves energy metabolism of myocardium due to activation of aerobic oxidation of carbohydrates and glucose catabolism in citric acid cycle.

Owing to influence upon carbohydrate metabolism, thiamine exerts expressed influence upon peripheral nervous system. At inflammatory diseases of peripheral nervous system, carbohydrate metabolism is disturbed with accumulation of incompletely oxidized products and development of acidosis. It causes the painful syndrome in neuritis, lumbago, and neuralgia. Thiamine is effective in these pathological states due to its ability to normalize carbohydrate and energy metabolism and stimulate acetylcholine synthesis. Vitamin B_1 decreases the level of glucose and lactic acid in the blood and, therefore, is used in the treatment for diabetes mellitus.

Thiamine stimulates the synthesis of GABA, serotonin, acetylcholine in central nervous system and therefore normalizes the processes of excitation and inhibition.

Besides, vitamin B_1 regulates the motility and secretion of gastrointestinal tract and activates epithelialization of skin and mucous membranes.

Vitamin B_1 deficiency is accompanied by development of neuritis, muscular weakness, and sensation disorders. In severe cases (disease beri-beri), the pareses and paralyses develop. Also, disorders of cardiovascular system, cardiac dystrophy, edemas, and dyspeptic disorders are observed.

Vitamin B_1 is taken orally and administered intramuscularly or intravenously drop-by-drop. The drug is readily absorbed from the intestine and penetrates different tissues. Thiamine undergoes phosphorylation in the liver.

Thiamine is used in the treatment for hypo- and avitaminosis (beri-beri), heart failure, tachyarrhythmias, ischemic heart disease, neuritis, lumbago, neuralgias, diabetes mellitus, dermatitis, eczema, and gastrointestinal diseases.

Thiamine is the most toxic drug among water-soluble vitamins. There is a risk of synaptic plegia in case of its intravenous administration due to ability of thiamine to form the complexes with different mediators. Synaptic plegia is accompanied by drop of blood pressure, cardiac arrhythmias, relaxation of skeletal muscles (including respiratory muscles), and inhibition of central nervous system.

Disorders of hepatic enzymes activity and development of allergic reactions up to anaphylactic shock are also possible due to therapy by thiamine.

Riboflavin (Vitamin B_2)

Significant emount of *riboflavin* is contained in liver, kidnays, eggs, dairy products, yeast, and cereals.

Vitamin B_2 is part of two coferments: FMN (flavin adenine mononucleotide) and FAD (flavin adenine dinucleotide). FMN and FAD are coenzynes of dehydrogenases and oxidases involved in redox processes. FMN and FAD are structural components of mitochondrial electron transport chain and thus involved in tissue respiration. Vitamin B_2 participates in metabolism of amino acids and ensures the functioning of epithelial tissues, eye lens, and brain.

Riboflavin is essential for synthesis and degradation of catecholamines both in central nervous system and in peripheral tissues. Vitamin B_2 promotes the synthesis of erythropoietin (hormone regulating the erythropoiesis). Riboflavin participates in metabolism of pantothenic and folic acids. Riboflavin promotes

synthesis of pyridoxal phosphate due to activation of pyridoxal kinase.

Riboflavin transforms short blue waves in longer green waves to which the retina is more sensitive. Therefore, riboflavin increases the visual acuity.

Vitamin B_2 also is necessary for vital activity of *E. coli*.

Riboflavin deficiency is accompanied by angular stomatitis, glossitis, keratitis, conjunctivitis, lens clouding, optic athrophy, appearance of cracks in the corners of the mouth and on the lips, eye pain, and photophobia. Hysteria, hypochondria, depression, feeling of the heat in the body, and muscular weakness develop in the patient. The gastrointestinal secretion decreases.

Riboflavin is taken orally and applied topically. *Riboflavin mononucleotide* is dosed parenterally. Riboflavin is readily absorbed from gastrointestinal tract and excreted by kidneys in unchanged form.

Riboflavin is used in the treatment for hypo- and avitaminosis, depression, hypochondria, feet pain, convulsions, skin and mucosa lesions, hair loss, night blindness, cataract, and digestive disorders.

Besides, vitamin B_2 is used in hypotrophy, hypochromic and hyperchromic anaemias, acute hypoxia (at acute heart failure, pneumonia, etc.), dysbiosis, and hepatitis.

Riboflavin can cause allergic reactions. Overdose of vitamin B_2 results in renal dysfunction owing to plugged renal tubules.

Nicotinic Acid and Nicotinamide (Vitamin B_3 or Vitamin PP)

Nicotinic acid is contained in cereals, yeast, buckwheat, liver, meat, milk, etc. Partly, vitamin PP is synthesized in intestine by saprophytic microorganisms.

Nicotinic acid is a part of NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate). NAD and NADP are primary components of mitochondrial and microsomal electron-transport chains. Thereby,

nicotinic acid is involved in all kinds of metabolism and detoxification of poisons.

Vitamin PP influences interrelation of inhibition and excitation processes in central nervous system. In such diseases as neurosis and hysteria, nicotinic acid promotes inhibition processes in CNS.

Nicotinic acid (but no nicotinamide) dilates vessels due to histamine release and activation of kinins system.

Vitamin PP exerts antiatherogenic effect owing to the inhibition of synthesis of low-density lipoproteins and very low-density lipoproteins. Nicotinic acid improves carbohydrate and energetic metabolism in the heart due to reduction of contents of pyruvic and lactic acids and increases the coronary blood circulation. Besides, vitamin PP increases the contents of glycogen and ATP in myocardium.

Nicotinic acid is essential for transformation of trans-retinol to cis-retinol which is involved in rhodopsin synthesis in eyes.

Nicotinic acid decreases the platelet aggregation owing to reduction of tromboxane A_2 synthesis and increases the activity of fibrinolytic system. Vitamin PP stimulates formation of normochromic erythrocytes and reticulocytes.

Nicotinic acid increases the synthesis and secretion of bile in liver and imroves digestion. Besides, vitamin PP improves detoxification function of liver by means of activation of conjugation and methylation of toxins.

Nicotinic acid deficiency results in pellagra. Main manifestations of pellagra include patological changes of mind (dementia – mental retardation, confusion, hallucinations, and cerebrospinal paralysis), digestive system (diarrhoea, stomatitis, and glossitis), and skin (dermatitis, pigmentation of exposed parts of the body).

Nicotinic acid and nicotinamide are administered parenterally or traken orally. Preparations of vitamin PP are used in the treatment for hypo- and avitaminosis, atherosclerosis (in daily doses 3–9 g), arteritis obliterans, Raynaud's disease, migraine, spasm of biliary or urinary tract, thrombosis, heart failure, ischemic heart disease,

hypoacid gastritis, gastroenteritis, hypochromic anemia, different intoxications, and for prevention of diabetus mellitus.

At therapy with nicotinic acid, much of the complications develop due to histamine release and kinin system activation: hypotension, dizziness, redness and itching of the skin, gastrointestinal hypersecretion, burning sensation during urination, etc. Long-lasting administration of nicotinic acid may result in fatty liver. To prevent this complication, products rich by methionine are consumed.

Pantothenic acid (Vitamin B_5)

Pantothenic acid is found in yeast, liver, eggs, fish eggs, cereals, and cauliflower. Partly, vitamin B_5 is synthesized by intestinal microflora.

Pantothenic acid is a part of coenzyme A transporting acetate and other acyl groups. Vitamin B_5 is essential for oxidation and synthesis of fatty acids, decarboxylation of ketoacids (pyruvic and α-ketoglutaric acids), synthesis of citric acid in Krebs' cycle, corticosteroids, acetylcholine, etc. Vitamin B_5 provides the normal structure of cell membranes and promotes the impulse transduction in cholinergic synapses.

Pantothenic acid deficiency is almost not detectable in humans.

Vitamin B_5 is used as *calcium pantothenate* to treat neuritis, neuralgia, allergy, respiratory diseases, postoperative intestinal atony, fatty liver, apathy, weakness, and disorders of neuromuscular transmission.

The drug is administered intramuscularly and taken orally. Vitamin B_5 is readily absorbed from gastrointestinal tract, does not undergo biotransformation in the body. The drug is excreted by kidneys (70 %) and liver (30 %).

Sometimes, therapy with calcium pantothenate is accompanied by dispeptic disorders.

Pyridoxine (Vitamin B_6)

Pyridoxine is found in yeast, cereals, legumes, bananas, meat, fish, liver, and kidneys. Also, this vitamin is synthesized by intestinal microflora.

Pyridoxal phosphate is the main active form of vitamin B_6. Pyridoxal phosphate participates in nitrogen metabolism. It promotes the absorption and distribution of amino acids, activates the processes of transamination, deamination, and decarboxylation of amino acids. For instance, decarboxylation of glutamic acid results in formation of γ-aminobutyric acid (GABA) – one of the main inhibitory mediators in central nervous system. Also, vitamin B_6 participates in transformation of tryptophan to serotonin and in conversion of tyrosine to dopamine and noradrenaline.

Products of deamination of amino acids include such acids as pyruvic, α-ketoglutaric, and oxaloacetic ones. These acids together with coenzyme A form acetylcoenzyme A which participates in number important biochemical reactions.

Pyridoxine exerts cardiotonic and hepatoprotective effects. Vitamin B_6 increases the synthesis of proteins and carbohydrates and activates hepatic detoxification function. Besides, vitamin B_6 stimulates erythro- and leukopoiesis.

Pyridoxine influences lipid metabolism. The vitamin promotes transformation of linoleic acid to nonsaturated arachidonic acid and decreases the level of cholesterol and lipids at atherosclerosis.

Hypovitaminosis B_6 is accompanied by stomatitis, convulsions, glossitis, seborrheic dermatitis on the face, etc.

Pyridoxine is used in the treatment for myocardiodystrophy, myocardiosclerosis, hepatitis, toxic anemia, agranulocytosis, radiation sickness, chorea, parkinsonism, neuritis, intoxications, etc. Also, pyridoxine is used at therapy by antitubercular drugs (isonicotinic acid derivatives) to prevent central nervous system disorders.

Pyridoxine and pyridoxal phosphate are administered subcutaneously, intramuscularly, intravenously and taken orally. At therapy by vitamin B_6, numbness of extremities, allergic reactions,

and increased gastric juice acidity may occur. Overdose of pyridoxine leads to disorders of protein, carbohydrate, and lipid metabolism, degenerative changes of central nervous system and parenchymatous organs.

Cyanocobalamin (Vitamin B_{12})

Cyanocobalamin is found in products of animal origin, especially in beef liver and kidneys. In human body, vitamin B_{12} is synthesized by intestinal bacteria. But this synthesis is not essential because vitamin B_{12} is mainly absorbed in small intestine.

In a body, cyanocobalamin is converted to cobamamide which is coenzyme of number reductases. These enzymes reduce folic acid to tetrahydrofolic acid that activates synthesis of nucleic acids and proteins and stimulates cell division. Thus, cobamamide exerts an anabolic effect. Besides, cobamamide exhibits membrano-stabilizing effect because it contributes to maintain bonds in unsaturated fatty acids. Cobamamide promotes synthesis of methionine from homocysteine. It is the source of methyl groups which are used for synthesis of choline, acetylcholine, etc. Also, cobamamide transfers methylmalonic acid to succinic acid which is essential for myelin synthesis.

Hypovitaminosis B_{12} leads to disorders of DNA synthesis. Most pronounced changes develop in rapidly proliferating tissues, e. g., cells of bone marrow (megaloblastic anemia develops). Digestive system is affected too: ahiliya and atrophy of mucous membrane of stomach develop. Paresthesia, pain along the nerves, and gait disturbance are pathological changes developed due to lesion of myelin synthesis in the nervous system.

Gastrointestinal absorption of vitamin B_{12} requires biermerin (Castle's intrinsic factor) which is synthesized by parietal cells of gastric mucosa. Also, biermerin prevents vitamin B_{12} absorption by intestinal bacteria. High concentration of vitamin B_{12} is accumulated in liver.

Cyanocobalamin is administered parenterally (intramuscularly or intravenously), cobamamide is taken orally. In the blood,

cyanocobalamin binds with special proteins transporting it to tissues. Cobamide penetrates blood-brain barrier better than cyanocobalamin. Vitamin B_{12} is accumulated in the liver; its half-life in the liver is about 12 months. The drug is excreted from the body mainly by kidneys (about 93 %).

Cyanocobalamin is used to treat pernicious anemia, hypochromic and hypoplastic anemias, radiculitis, degenerative changes in the central nervous system, fatty liver, radiation sickness, hypotrophy in children, etc.

Side effects of cyanocobalamin are allergic reactions, tachycardia, heart pain, lipid infiltration of liver, and increased excitability.

Folic acid (Vitamin B_c)

Folic acid is found in green peas, carrot, potatoes, egg yolk, liver, meat, fish, etc. Intestinal microflora also synthesizes folic acid.

In human body, folic acid is reduced to tetrahydrofolic acid. Vitamins B_{12}, C, and biotin are essential for synthesis of tetrahydrofolic acid. Tetrahydrofolic acid is cofactor of some enzymes participating in transport of one-carbon radicals (methyl group, methylene group, hydroxymethyl group, etc.). One-carbon groups are essential for synthesis of purine and pyrimidine bases, proteins, and amino acids. Therefore, tetrahydrofolic acid activates cellular division and growth and stimulates regenerative processes. Tetrahydrofolic acid participates in such processes as transformation of serin to glycine, synthesis of methionine from homocystein, etc.

Folic acid deficiency is closely releated to deficiency of cyanocobalamin. Clinical manifestations of deficiency of both vitamins are very similar. A difference is that the neurological disturbances are more common at cyanocobalamin deficiency. Patological changes in peripheral blood and bone marrow are similar and include megaloblastic and macrocytic anemias. Besides, leukopenia and lesions of gastrointestinal tract are observed.

Folic acid is absorbed in small intestine and deposited in the liver. From the body, folic acid is excreted by kidneys and liver in unchanged form.

Folic acid is used in the treatment for macrocytic, megaloblastic, hypochromic, and hypoplastic anemias, leukopenia, agranulocytosis, sprue, thrombocytopenia, enteritis, hypotrophy in children, wounds, burns, etc.

Dispeptic disorders, insomnia, disorders of renal function, and neoplasm are side effects occuring at therapy by folic acid. Prescription of folic acid to elderly patients who have a propensity to cancer is especially dangerous.

Ascorbic acid (Vitamin C)

Significant amount of *ascorbic acid* is found in vegetables, fruit, berries, pine needles, dog-rose, blackberry, etc.

Main effects of ascorbic acid are associated with its role in redox processes. Transformation of ascorbic acid to dehydroascorbic acid is a reversible process which provides transport of hydrogen ions.

Ascorbic acid catalyzes the following processes:

– transformation of folic acid to tetrahydrofolic acid which participates in synthesis of nucleic acids and proteins;

– synthesis of hyaluronic acid which decreases the permeability of the vessel wall;

– synthesis of noradrenaline from tyrosine;

– synthesis of steroid hormones from cholesterol;

– synthesis of collagen, which is a structural component of the cartilage, bones, and other connective tissues;

– synthesis of carnitine, which promotes utilization of fatty acids as the source of energy.

Besides, ascorbic acid promotes absorption of iron in the gastrointestinal tract due to reduction of Fe^{3+} to Fe^{2+}. Vitamin C stimulates functional activity of the respiratory chain in hepatocytes and increases detoxificating and synthetic functions of the liver.

Ascorbic acid increases the synthesis of interferon and antibodies and activates phagocytosis and leukocyte chemotaxis. Thus, ascorbic acid activates non-specific immunity.

High doses of ascorbic acid inhibit the synthesis and secretion of insulin.

Vitamin C exerts antioxidative activity by means of reduction of free oxygen radicals in the presence of glutathione and α-tocopherol. Also, vitamin C exhibits antiatherosclerotic effect.

Deficiency of ascorbic acid is accompanied by hypo- and avitaminosis (scurvy). Symptoms of scurvy include fatiguability, dryness of skin, hemorrhagic rash, gingivitis, bleeding from the gums, losing teeth, hemorrhages in the skeletal muscles, pain in the extremities, disturbances of internal organs functions (liver, heart, etc.), and decreasing of immunity.

Ascorbic acid is taken orally and administered intramuscularly or intravenously. Absorption of ascorbic acid begins in oral cavity and continues in intestine with participation of glucose. Maximum concentration in the blood is observed in 4 hours. From the blood, ascorbic acid penetrates better into the leukocytes, platelets, pituitary, eye, adrenal glands, and liver.

Biotransformation of ascorbic acid occurs in the liver. Metabolites are excreted mainly by kidneys.

Ascorbic acid is used to prevent and treat scurvy and hypovitaminosis in winter-spring season, in complex treatment for viral and bacterial infections, at stress, hypoxia, metabolic and respiratory acidosis, hemorrhagic syndrome, inflammatory and allergic diseases, hypochromic anemia, atherosclerosis, acute hypotension, radiation sickness, etc. Ascorbic acid is prescribed to patients who are long-time treated by non-steroid anti-inflammatory drugs and antibiotics (tetracyclines, etc.) which eliminate vitamin C from the body.

Therapeutic doses of ascorbic acid are well tolerated by patients. Long-time intake of high doses can cause damage of pancreas with hyperglycemia, damage of kidneys, and increase of blood pressure. Excess of ascorbic acid promotes the tendency to thrombosis,

hemolysis of errhythrocytes, formation of urinary stones, irritability, increased synthesis of estrogenes, and allergic reactions.

Rutin (Vitamin P)

Several substances – bioflavonoids belong to vitamin P. Bioflavonoids are found in citrus, blackberry, dog-rose, chokeberry, green tea, etc.

Rutin exerts antioxidant effect. Vitamin P promotes transformation of ascorbic acid to dehydroascorbic acid which easily penetrate the cells. Also, rutin prevents the transformation of dehydroascorbic acid to diketogulonic acid (it is inactive metabolite of ascorbic acid). Vitamin P promotes accumulation of ascorbic acid in the adrenal glands, liver, and other organs and slows down excretion of vitamin C from the body.

Rutin is synergist of ascorbic acid in its influence upon vascular wall. Vitamin P decreases vascular permeability due to inhibition of hyaluronidase activity. Rutin prevents the oxidation of adrenaline and free fatty acids and increases the resistance of tissues to radiation.

Rutin deficiency is accompanied by increased vascular permeability.

Rutin is used in the treatment for angiasthenia, ischemic heart disease, cholestasis, and venous insufficiency of the lower limbs. Drug is taken orally.

Therapy by rutin is not accompanied by side effects.

Methylmethionine (vitamin U)

Methylmethionine is found in tomatoes, asparagus beans, cabbage, celery, etc. Vitamin U is donator of methyl groups. Drug exerts anti-ulcer effect. Indications for use of methylmethionine are ulcer disease of stomach and duodenum, gastritis, and ulcerative colitis.

Drugs of Liposoluble Vitamins

Retinol (Vitamin A)

Vitamin A brings together a number of compounds: *retinol* (vitamin A_1), *dehydroretinol* (vitamin A_2), *retinal*, and *retinoic acid*. Vitamin A is found in animal products: cod-liver oil, liver, butter, yolk, etc. There are products of plant origin (carrots, parsley, buckthorn, black chokeberry, dog-rose, etc.) which contain provitamin A carotene. In human body, carotene is converted to vitamin A. Two molecules of vitamin A are synthesized due to hydrolysis of one carotene molecule.

Cells of target organs contain specific receptors, which interact with retinol-binding protein. This complex penetrates the nucleus and activates genes responsible for synthesis of proteins and structural components of tissues.

Each retinoid has its own value in a body. Thus, retinol provides growth, tissue differentiation, and normal function of reproductive system. Retinoic acid is essential for differentiation of epithelium and regulates activity of calcitriol receptors. Retinal provides normal function of retina, etc.

Vitamin A is essential for activation of phospho-adenosine-phosphosulfate which is the part of:

– mucopolysaccharides: heparin, hyaluronic acid, chondroitin sulfate, and other components of connective tissue;

– sulfate-contaning cerebrosides;

– taurine, which is essential for synthesis of somatotropin and for providing synaptic transmission of impulses;

– hepatic enzymes providing detoxification function.

Retinol participates in the synthesis of somatomedins A, B, and C, which promote protein synthesis in muscles, inhibit lipolysis, and provide the incorporation of proline to collagen. Also, retinol is essential for incorporation of phosphates and thymidine in DNA molecules.

Vitamin A stimulates the synthesis of steroid hormones and takes part in formation and functioning of thymus, spleen, and lymphoid tissue. This vitamin is essential for synthesis of

immunoglobulins, interferon, and lysozyme. Vitamin A supports the activity of phagocytes.

Retinol stimulates the synthesis of enzymes in epithelial cells and prevents the excessive epidermidalization.

Because retinol participates in rhodopsin synthesis, it is important for supporting visual acuity and for eye adaptation to the dusk. Rhodopsin is a photosensitive pigment contained in rods – cells which are sensitive to low intensity light. Under the influence of light, rhodopsin splits into retinal and opsin. This process causes impulse generation. Dehydrogenase transforms the retinal to retinol. Resynthesis of rhodopsin occurs in dark periods that increases the visual acuity in low light.

Vitamin A deficiency is accompanied by development of nocturnal amblyopia (night blindness). Also, skin epithelium and mucous membranes are affected: different types of epithelium are transformed to stratified squamous epithelium and keratinization processes are increased. Skin becomes dry, there are rashes. The mucous membranes of eyes are affected: cornea becomes dry (xerophthalmia) and softened (keratomalacia). Severe cases of retinol deficiency may lead to total blindness.

Vitamin A deficiency is also accompanied by lesions of respiratory, gastrointestinal, and urogenital system. Damages of skin and mucous membranes and immunosuppression promote infectious diseases.

Retinol and carotenoids are readily absorbed from gastrointestinal tract. Fatty food and bile are essential for their absorption. In blood, vitamin A is binded with specific protein synthesized in liver. This complex interacts with special receptors of cellular membranes. Owing to this interaction, the free retinol penetrates the cells. Excess of vitamin A is deposited in a liver, there it undergoes biotransformation with formation of active and inactive metabolites. Metabolites of retinol are excreted by the kidneys and intestine.

Vitamin A is used to treat and prevent hypo- and avitaminosis, in the treatment for infectious diseases (together with vitamin C),

rickets (together with vitamin D), night blindness, keratitis, xerophthalmia, psoriasis, dermatitis, acne, inflammatory diseases of respiratory and gastrointestinal tracts, burns, frostbite, trophic ulcers, etc. Retinol is also used in stomatology.

Excessive intake of vitamin A leads to hypervitaminosis. Acute poisoning by retinol is manifested by convulsions and paralysis. Symptoms of chronic poisoning by vitamin A are worsen vision, photophobia, abdominal pain, dry skin, increased size of liver and spleen, increased intracranial pressure with headache, nausea, vomiting, etc. At appearance of such symptoms, therapy by vitamin A should be stopped. A patient is treated by osmotic diuretics (to reduce intracranial pressure), glucocorticoids, and tocopherol.

Ergocalciferol (Vitamin D)

Vitamin D includes *ergocalciferol* (vitamin D_2) and *cholecalciferol* (vitamin D_3). Ergocalciferol is substance of plant origin, while cholecalciferol is synthesized in skin under influence of ultraviolet. Significant amount of vitamin D is found in the liver of tuna, cod, halibut, and kit. Cow's milk and egg yolks are also rich in vitamin D.

Vitamins D_2 and D_3 are pharmacologically inactive. These vitamins are converted to active metabolites in kidneys. Metabolites of vitamin D (e. g., calcitriol) are hormone-like substances regulating metabolism of calcium and phosphorus.

Calcitriol penetrates inside of the target cells and binds to cytoplasmic receptors. Complex calcitriol-receptor enters the nucleus and causes the derepression of genes responsible for synthesis of specific and non-specific proteins.

Thus, in the intestinal mucosa, calcitriol activates the synthesis of specific protein binding calcium and non-specific proteins promoting absorption of calcium, magnesium, and phosphorus. Besides, vitamin D stimulates the synthesis of alkaline phosphatase in the intestinal mucosa. This enzyme participates in the intestinal absorption of calcium and synthesizes the calbindin binding

excessive amount of calcium and preventing its damaging influence upon the cells.

In bones, vitamin D activates the synthesis of alkaline phosphatase which promotes calcium capture from the blood and its deposition in the growth zone of bones. In osteoclasts, vitamin D increases the synthesis of osteocalcin – protein which is matrix for ossification. Besides, vitamin D stimulates the synthesis of collagen in bones. It is necessary to note, that active metabolites of vitamin D also take part in resorption of calcium in diaphysis due to formation of water-soluble calcium citrate.

In epithelial cells of renal tubules, vitamin D stimulates synthesis of calcium-binding protein. It provides calcium reabsorption in proximal convoluted tubules. Also, vitamin D increases the renal synthesis of alkaline phosphatase (participates in calcium capture form of the lumen of tubule) and some proteins providing reabsorption of sodium, amino acids, citrate, phosphates, and carnitine.

Vitamin D stimulates secretion of thyroid-stimulating hormone and interleukin-1, and inhibits the formation of γ-globulin and interleukin-2.

Vitamin D deficiency in children results in rickets. The manifestations of rickets include broken calcification of bones, deformation of spine and lower extremities, muscular hypotonia, and retardation of growth and development of child. Deficiency of vitamin D in adults, results to osteomalacia and osteoporosis.

Absorption of vitamin D occurs in small intestine. In blood, vitamin D binds to α-globulin and this complex is transported to organs. Vitamin D is deposited in bones, fatty tissues, liver, mucous membranes of small intestine, and other organs. Vitamin D undergoes hepatic biotransformation with formation of both active and inactive metabolites. Inactive metabolites of vitamin D undergo mainly intestinal and, in small degree, – renal excretion.

Elimination of vitamin D from organism is gradual, about 34 % administered dose is eliminated for 21 days. Therefore, there is

danger of accumulation of vitamin D in the body owing to its repeated intake.

The following drugs of vitamin D are used in medicine: *ergocalciferol, calcitriol, alfacalcidol, cholecalciferol (Vigantol), cod liver oil*, etc. These drugs are used mainly to prevent and treat rickets. Preventive dose for chidren under 1 year is 400–500 IU a day. To treat rickets, vitamin D is dosed individually starting from 5,000 IU a day.

Besides, vitamin D is used in the treatment for osteomalacia, osteoporosis, bone fractures, tuberculoderma, psoriasis, and hypocalcemia (in patients with hypoparathyroidism, chronic renal failure, adminsitration of large volume of citrate blood).

At pathologies when fast effect is necessary, drug of choice is calcitriol, which is administered together with calcium-containing drugs.

Overdose of vitamin D results in acute or chronic hypervitaminosis which is accompanied by intensive calcium absorption in intestine and bone resorption. Due to these processes, following pathological changes are observed: hypercalcemia and calcification of soft tissues, vascular wall, lungs, intestine, kidneys, heart valves, etc. Increased formation of free oxygen radicals leads to lesions of cellular and subcellular membranes. It is accompanied by impairment of cardiac contractility, development of necrotic foci, and arrhythmias. Flaccidity, drowsiness, sudden anxiety, and convulsions are manifestations of damage of central nervous system.

To treat vitamin D hypervitaminosis, glucocorticoids, vitamin E, magnesium- and potassium-containing drugs, ascorbic acid, retinol, and thiamine are used. Besides, symptomatic therapy is performed.

Tocopherol (Vitamin E)

There are *α*-, *β*-, and *γ-tocopherols*. α-Tocopherol is the most active among them. Vitamin E is contained in cereals (oats, rice, rye, etc.), meat, fats, eggs, and milk. For humans, main sources of tocopherol are vegetative oils.

Tocopherol takes part is synthesis of lipids, mucopolysaccharides, and different proteins (collagen, contractile proteins of skeletal and smooth muscles, hepatic enzymes, vasopressin, coenzyme Q, heme, gonadotropins, etc.).

Tocopherol is one of the most potent antioxidants. Vitamin E exerts marked protective effect on phospholipids of cellular, mitochondrial, and lysosomal membranes. Tocopherol protects chromosomes from mutagenic influence of free radicals. Free radicals play important role in pathogenesis of autoimmune and inflammatory diseases, hypoxia, hypertermia, shock, excessive stress, viral and bacterial infectious diseases, etc.

Hypovitaminosis of vitamin E in humans is not registered. In animal models with complete deprivation of vitamin E, following pathological changes are observed: suppressing of spermatogenesis, suppressing of implantation, abortions, and degeneration of myocardium and skeletal muscles.

Tocopherol is administered intramuscularly or taken orally. Vitamin E is absorped in small intestine. Maximum concentrations of vitamin are observed in fat tissue, liver, muscles, and retina. Unconverted vitamin E is excreted mainly through intestine. At parenteral administration, about 1/3 administered dose of vitamin E is metabolized and excreted with the urine.

Tocopherol is used in the treatment for reccurent abortions, violation of menses, juvenile bleeding, atherosclerosis, heart failure, coronary insufficiency, anemias, arthrosis, myocardiodystrophy, epilepsia, radiation sickness, etc.

Long-lasting intake of vitamin E is accompanied by reduction of vitamin K activity, gastrointestinal bleeding, toxic influence upon the blood (affection of neutrophiles and thrombocytes), hepatotoxicity, and nephrotoxicity.

Naphthoquinone (Vitamin K)

Group of naphthoquinones includes *phylloquinone* (vitamin K_1) and *menaquinone* (vitamin K_2). Vitamin K_1 is substance of plant origin. Phylloquinone is contained in spinach, cabbage, pumpkin, etc. Menaquinone is synthesized by liver of animals and by intestinal microflora. Activity of vitamin K_1 is higher than activity of vitamin K_2. *Vicasolum* (vitamin K_3 or menadione) is synthetic water-soluble analogue of vitamin K.

In liver, vitamin K stimulates a synthesis of prothrombin (factor II), proconvertin (factor VII, kappa factor), Christmas factor (factor IX), and Stuart-Prower factor (factor X, or prothrombinase). Besides, vitamin K promotes the synthesis of ATP, creatine phosphate, and some enzymes.

Most commonly, vitamin K deficiency develops in result of intestinal or hepatic diseases and is accompanied by bleeding, hemorrhagic diathesis due to reduction of synthesis of K-dependent factors of blood clotting.

Preparations of vitamin K are administered intramuscularly or taken orally. Bile acids are essential for intestinal absorption of vitamin K.

Vitamin K is used in the treatment for bleeding, hemorrhagic diathesis, hepatitis, cirrhosis, diarrhoea, ulcer disease of stomach and duodenum, uterus bleeding. Also, vitamin K drugs are administered prior and after surgical operations to prevent hemorrhages. Therapeutic effects of vitamin K appear in several hours after drug administration.

Ussually, side effects do not appear during therapy with vitamin K. But parenteral administration of vitamin K to newborns can cause hemolytic anemia and jaundice.

Non-Vitamin Cofactors

Non-vitamin cofactors are endogenous metabolites participating in regulation of body metabolism. Partly, these substances are taken with food so that have sertain similarity to vitamins (sometimes, symptoms of their deficiency are observed). There are the following

non-vitamin cofactors: *lipoic acid* and *lipamide, carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid), pangamic acid (vitamin B_{15}), choline, inosine (Riboxin), adenosine monophosphate (AMP, Phosphaden),* and *potassium orotate.*

Carnitine is synthesized in the liver and kidneys by means of hydroxylase. Partly, carnitine is taken with ingredients of animal origin. Medical preparation carnitine chloride is obtained by synthetic way. In a body, carnitine catalyzes synthesis of acetyl-CoA which is essential for synthesis of pyruvate oxidase participating in gluconeogenesis.

Carnitine deficiency is accompanied by disorders of amino acid metabolism and protein synthesis, slowdown of retardation of growth and development, hypoglycemia, disorders of synthesis of neurotransmitters (acetylcholine, etc.) and phosphatidyl choline (main component of surfactant). Mitochondrial long chain fatty acid β-oxidation is affected that leads to decrease of ATP synthesis. Carnitine deficiency leads to deposition of lipids in skeletal muscles and myocardium that affects their contractility.

Besides, carnitine restricts lipid oxidation and formation of hydroperoxides of fatty acids and, therefore, keeps structure of cellular membranes.

Carnitine is used in the treatment for immature infants who are on artificial nutrition, haemodialyzed patients (in this case, carnitine is excreted from the body and acyl ethers are accumulated), hypoxia, diphtheria, therapy with valproic acid, intractable diarrhea, cardiomyopathy, and infant respiratory distress syndrome. Besides, carnitine is used to treat organic acidemia (elevation of concentration of organic acids in the blood), cardiopulmonary failure, and chronic hypoxia. At mild and moderate thyrotoxicosis, carnitine improves patient status and promotes body weight gain.

As a rule, 1 teaspoon of 20 % carnitine solution is taken orally 2–3 times a day 30 minutes prior meal. Course of treatment lasts 2–3 months. Carnitine is well tolerated by patients. Sometimes, stomach pain is possible that requires to decrease the drug dose.

Lipoic acid is synthesized in a body and, partly, taken with meat products. It is cofactor of number of enzymes participating in carbohydrate and lipid metabolism. Lipoic acid activates citric acid cycle, decreases concentration of lactic acid, eliminates intracellular acidosis, and stimulates synthesis of CoA. Lipoic acid exerts hepatoprotective effect restricting lipid deposition in liver. Also, lipoic acid activates protein metabolism. Due to its ability to transform to dihydrolipoic acid, it takes part in mitochondrial transport of hydrogen. Lipoic acid contains thiol groups, thereby it normalizes lipid peroxidation and transformation of oxyhemoglobin to methemoglobin.

Lipoic acid is manufactured in tablets containing 0.012 or 0.025 g or in ampoules containing 2 ml of 0.5 % solution (for intramuscular administration).

There are the following therapeutic indications for lipoic acid:

– diabetes mellitus;

– acute and chronic hepatites;

– acute poisoning by hepatotoxic substances;

– hypotrophia in children;

– prevention of hypercholesterolemia.

Side effects of lipoic acid include dyspepsia, allergic reactions, increased gastric secretion, etc.

Inosine (Riboxin) is purine derivative – precursor of ATP. The drug activates nucleic acid synthesis and tissue regeneration (especially, in myocardium and gastrointestinal tract), icreases stroke volume of heart, improves tissue microcirculation, and decreases platelet aggregation. Riboxin is dosed orally 0.2 g 3–4 times a day or intravenously slowly 10 ml of 2 % solution. The drug is used in the treatment for following diseases:

– ischemic heart disease;

– cardiac arrhythmias;

– hepatitis and cirrhosis of liver;

– ulcer disease of stomach and dupdenum;

– poisoning by xanthines;

– porphyria cutanea tarda.

Ribaxin is well tolerated by patients. Its possible side effects are gout exacerbation, itching, and skin hyperemia.

Potassium orotate is pyrimidine precursor exerting anabolic effect. The drug is taken orally in dose 0.5 g 2–3 times a day. Course of treatment lasts 3–5 weeks. Therapeutic indications for otassium orotate are the follows:

– hypothrophy in children;

– chronic heart failure, myocardial infarction, cardiac arrhythmias;

– toxic hepatitis;

– leukopenia;

– hypochromic anemia;

– poorly healing ulcers and wounds;

– progressing muscular dystrophy.

Adenosine monophosphate (AMP, Phosphaden) is ATP precursor. The drug penetrates cells and activates synthesis of ATP. Phosphaden is part of enzymes activating redox processes. The drug is dosed orally 0.025–0.05 g 3–4 times a day or intramuscularly 1 ml of 2 % solution. Its clinical indications are the follows:

– poisoning by lead with symptoms of polyneuritis;

– acute intermittant porphyria;

– chronic endarteritis and thrombophlebitis (Phosphaden dilates vessels and decreases platelet aggregation);

– hepatic diseases;

–ischemic heart disease and chronic heart failure.

The drug is well tolerated by patients. Its possible side effects are dyspepsia, dizziness, tachycardia, and allergic reactions.

Role of Zinc and Copper in Human Body

Zinc is essential for synthesis more than 90 enzymes of human body. Zinc activates enzymes controling DNA synthesis, improves protein metabolism, activates tissue regeneration, and promotes body weight gain. This microelement is essential for function of insulin, sex hormones, pancreatic carboxypeptidase, angiotensin-converting enzyme, alcohol dehydrogenase in liver and eye retina, alkaline

phosphatase in bones, intestine and kidneys. Zinc maintains stability of cellular membranes, restricts histamine release from basophils and formation of free radicals. Zinc participates in regulation of functions of lymphoid tissue and immune system.

In medicine, this microelement is used in form of *zinc oxide* and *zinc sulfate (Zincteral)* for oral intake after meal. Indications for zinc-containing drugs are the follows:

– prevention and treatment of hypodynamia;

– pregnancy (especially last trimester);

– premature infants;

– renal and hepatic diseases, hypovitaminosis D, burns, enteritis, psoriasis, helmintoses and other pathological states which are accompanied by hypozincemia;

– acute respiratory infections.

Copper is cofactor of number enzymes. Copper is essential for gastrointestinal absorption of iron and its incorporation into heme, porphyrin synthesis, and maturation of reticulocytes. Copper activates superoxide dismutase – enzyme interfering free radical reactions and protecting cellular membranes from damage.

Copper sulfate is dosed orally to prevent and treat hypocupremia (commonly observed in premature infants) and to treat hypochromic anemias. Besides, copper-containing drugs are prescribed for children under parenteral nutrition and who feeding by cow milk.

Antivitamins

Antivitamins are substances which violate the use of vitamins by body with development of vitamin deficiency. Antivitamins are divided into two groups:

1) antivitamins that disrupt vitamins or bind to vitamin molecules with formation of inactive forms: *avidin* (protein of raw egg), *thiaminase*, *ascorbinase*, and *lipoxidase;*

2) antivitamins which are structurally similar to vitamins and due to this can replace vitamins from bioactive compounds:

methotrexate, *neodicumarin*, *quinacrine*, *quinine*, *isoniazid*, and *lead*.

Avidin is protein of raw eggs. Avidin can bind with vitamin H (biotin) with formation of water insoluble complex which lacks bioactivity.

Thiaminase disrupts vitamin B_1. Significant amount of thiaminase is contained in guts of fish and shellfish, in ferns, etc. It is proved, that mild forms of B_1 hypovitaminosis which occured in Japanese is due to intestinal flora which produced thiaminase.

Ascorbinase is contained in different plants. Ascorbinase metabolizes ascorbic acid to dehydroascorbic acid which is easily destroyed under influence of temperature and acid environment.

Lipoxidase is contained in soybeans. It destroys carotine and promotes the development of vitamin A hypovitaminosis.

Antivitamins of another group are structural vitamin analogues which significantly influence a body metabolism. Such substances have not own bioactivity but can restrict or eliminate effects of vitamins. Thus, there are both competitive and non-competitive antagonism between vitamin and antivitamin.

Methotrexate is antagonist of folic acid. Methotrexate affects synthesis of active coenzyme form of folic acid – tetrahydrofolic acid which is essential for synthesis of purine bases. Due to this, DNA and RNA synthesis slows down that violates cells division. Because neoplastic cells rapidly proliferate, they are quite susceptible to methotrexate influence. Therefore, methotrexate is used in the treatment for leucosis (especially in children) and breast cancer.

Antagonists of vitamin K (or indirect anticoagulants) are syncumar, neodicumarin, warfarin, and phenylin. These drugs affect synthesis of K-dependent factors of blood cloting: prothrombin (II factor), proconvertin (VII factor), Christmas factor (IX factor), and Stuart-Prower factor (X factor). Indirect anticoagulants are used to prevent thrombosis. There are the following indications for their use.

1. Prevention and treatment of venous thrombosis, thrombophlebitis, myocardial infarction, and ischemic stroke.

2. Prevention of thrombosis in postoperative period.

3. Prevention of thrombosis and thromboembolia in patients with rheumatic heart disease.

4. Prevention of thrombosis after angioplasty, prosthetic heart valves.

5. Prevention of thrombosis after discontinuation of therapy with directly acting anticoagulants.

Isoniazid is derivative of isonicotinic acid which used in the treatment for tuberculosis. Isoniazid is antagonist of pyridoxine. It affects the formation of coenzyme form of vitamin B_6 – pyridoxal phosphate which is essential for metabolism of amino acids and synthesis of certain neurotransmitters (GABA, serotonin, etc.). Reduced synthesis of pyridoxal phosphate is a cause of such side effects of isoniazid as peripheral neuropathy, seizures, hyperreflexia, increased frequency of seizures in patients with epilepsy, etc. To prevent these side effects, vitamin B_6 is prescribed together with isoniazid.

Antimalarial drugs quinene and mepacrine (quinacrine) suppress effects of riboflavin (vitamin B_2). These drugs affect the flavin enzymes that facilitates its activity against malarial plasmodium, trichomonas, leishmania, and balantidium.

Plumbum (lead) is noncompetitive antagonist of vitamin B_{12}. Lead inhibits activity of intrinsic Castle's factor and affects gastrointestinal absorption of cyanocobalamin.

Antagonism between different vitamins is also known. Retinol is antagonist of calciferol. There are complex relationships between retinol and tocopherol. It is known, that tocopherol prevents oxidation of retinol. But on the other hand, significant amount of vitamin A reduces hepatic reserve of tocopherol.

Pyridoxine is a thiamine antagonist. Excess of thiamine in food increases the symptoms of B_6 hypovitaminosis. Neuronal toxicity of high doses of thiamine is eliminated by pyridoxine.

Table 10 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Thiamini bromidum	Orally 0.002 58–0.012 9 g; Intramuscularly 0.03–0.06 g	Tablets 0.002 58 or 0.012 9 g; ampoules 3 % or 6 % – 1 ml
Acidum nicotinicum	Orally 0.02–0.05 g; intramuscularly 0.01 g; intravenously 0.05 g	Tablets 0.05 g; ampoules 1 % – 1 ml
Pyridoxini hydrochloridum	Orally, subcutaneously, intramuscularly or intravenously 0.025–0.05 g	Tablets 0.005 or 0.01 g; ampoules 1 % or 5 % – 1 ml
Acidum folicum	Orally 0.005 g daily	Tablets 0.001 g
Cyanocobalaminum	Subcutaneously, intramuscularly or intravenously 0.000 1–0.000 5 g 1 time a day or 1 time per 2 days	Ampoules 0.003 %, 0.01 %, 0.02 % and 0.05 % – 1ml
Acidum ascorbinicum	Orally 0.05–0.1 g; intramuscularly or intravenously 0.05–0.15 g	Dragee 0.05 g; tablets 0.025; 0.05 or 0.1 g; ampoules 5 % or 10 % – 1 or 2 ml
Retinoli acetas	Orally or intramuscularly 33 000–100 000 IU daily	Coated tablets 33 000 IU; ampoules with oil solution (25 000; 50 000 or 100 000 IU in 1 ml)
Ergocalciferolum	Orally 10 000–100 000 IU daily	Vials with 0.125 % or 0.5 % oil solution (50 000 or 200 000 IU in 1 ml consequently)
Tocopheroli acetas	Orally or intramuscularly 0.015–0.15 g daily	Vials with 5 %, 10 % or 30 % oil solution – 10; 20 or 50 ml; ampoules with 5 %, 10 % or 30 % oil solution – 1 ml
Vicasolum	Orally 0.015 g; intramuscularly 0.01 g	Tablets 0.015 g; ampoules 1 % – 1 ml

Step 1. Tasks for Self-Control
Vitamins

1. A 39-year-old man appealed to a hospital. Recently he noticed susceptibility to infectious diseases and impairment of twilight vision. During the examination a doctor diagnosed hyperkeratosis. What vitamin should be prescribed?

A. Tocopherol acetate.
B. Pyridoxine hydrochloride.
C. Riboflavin.
D. Ergocalciferol.
E. Retinol acetate.

2. A patient came to a doctor with complaints of twilight adaptation impairment (night blindness). What vitamin drug to be prescribed to the patient for the restoration of his sight?

A. Tocopherol acetate.
B. Vicasolum.
C. Pyridoxine hydrochloride.
D. Thiamine chloride.
E. Retinol acetate.

3. The deficiency of prothrombin in blood was detected during a preoperative examination of a patient. What drug is needed for the preliminary use for reducing blood loss during operation?

A. Vicasolum.
B. Thrombin.
C. Aminocaproic acid.
D. Phenylinum.
E. Contrycal.

4. A patient who was previously ill with mastectomy as a result of breast cancer was prescribed radiation therapy. What vitamin drug has marked radioprotective action caused by antioxidant activity?

A. Folic acid.
B. Ergocalciferol.
C. Thiamine chloride.
D. Tocopherol acetate.
E. Riboflavin.

5. A patient suffers from hemeralopia. Which of the suggested substances will have curable effect?

A. Carnitine.

B. Keratin.

C. Carotin.

D. Carnosine.

E. Creatine.

6. A patient who has mastectomy because of the mammary gland cancer, is prescribed a course of radiotherapy. What vitamin drug has antiradiation effect caused by antioxidant activity?

A. Follic acid.

B. Ergocalciferol.

C. Riboflavin.

D. Cyanocobalamin.

E. Tocopherol acetate.

7. In experiment on fibrocytes culture it is established, that addition of cells of one of vitamins in an inhabitancy strengthens formation of fibrous fibers. This effect is oppressed with transcription inhibitors. What vitamin is used?

A. Retinol.

B. Tocopherol.

C. Thiamine.

D. Riboflavin.

E. Rutin.

8. A 28-year-old patient suffers from hemeralopia (night blindness). What vitamin should be prescribed to him?

A. Ascorbic acid.

B. Cyanocobalamin.

C. Retinol.

D. Tocopherol.

E. Thiamine.

9. On the ground of clinical presentations a patient was prescribed pyridoxal phosphate. This medication is recommended for correction of the following processes:

A. Oxidative decarboxylation of ketonic acids.

B. Desamination of purine nucleotides.

C. Protein synthesis.

D. Synthesis of purine and pyrimidin bases.

E. Transamination and decarboxylation of amino acids.

10. A patient presents with twilight vision impairment. Which of the following vitamins should be administered?

A. Ascorbic acid.

B. Cyanocobalamin.

C. Retinol acetate.

D. Nicotinic acid.

E. Pyridoxine hydrochloride.

11. Before tooth extraction a patient was advised to take a certain drug for haemorrhage prevention. What drug was advised?

A. Asparcam.

B. Vicasolum.

C. Heparin.

D. Magnesium sulfate.

E. Dimedrol.

HORMONAL DRUGS

Hormonal drugs include preparations of natural hormones obtained from endocrine glands of animals, its synthetic analogues and antagonists.

Together with nervous system, endocrine system participates in regulation of organism homeostasis. In neuroendocrine complex, there are three levels of regulation: hypothalamus, pituitary, and peripheral endocrine glands.

In response to chemical stimuli, hypothalamus secretes low-molecular-weight peptides. Some of them (releasing-factors, or liberins) stimulate secretion of anterior pituitary hormones; other peptides (statins) inhibit it. Secretion of hypothalamic and pituitary hormones is regulated by means of negative feedback. Thus, reduction of secretion of certain pituitary hormone leads to increase of secretion of corresponding hypothalamic releasing-factor. And

vice versa, increase of certain pituitary hormone concentration results in reduction of corresponding liberin secretion.

Second level regulating body neuroendocrine functions is anterior pituitary. It secretes several tropic hormones controling activity of peripheral endocrine glands. Some of them (somatotropin or growth hormone) directly influence tissues.

Posterior pituitary deposits two hypothalamic hormones: vasopressin and oxytocin which directly influence the functions of target tissues.

Third level of regulation of neuroendocrine complex includes peripheral endocrine glands: thyroid and parathyroid glands, adrenal cortex, testes, ovaries, and pancreas. Their hormones interact with specific receptors in target tissues. These receptors are located in cell membranes as well as intracellularly (in nucleus, in cytoplasm). Due to interaction with these receptors, hormones change enzymatic acitivity, ion transport, peptide synthesis, and other metabolic processes. Thus, hormones regulate growth, development, reproduction, protective properties, and other functions of organism.

According to chemical structure, hormones are divided into 3 groups.

1. Peptide hormones: hormones of hypothalamus, pituitary, pancreas, parathyroid, and thyroid (calcitonin) glands.

2. Steroid hormones: adrenocortical and sex hormones.

3. Derivatives of amino acids: thyroid hormones (thyroxine, triiodothyronine) and hormones of adrenal medula (adrenaline, noradrenaline).

In medicine, hormonal drugs are used for the following purposes:

1) substitutive and stimulative therapy in cases of certain hormonal insufficiency. Thus, insulin is used for substitutive therapy at I type of diabetus melitus; glibenclamide is used for stimulative therapy at II type of diabetus melitus (it stimulates secretion of insulin by pancreas);

2) inhibitive therapy in cases of hyperactivity of certain gland (e. g., somatostatin is used to reduce somatotropin secretion by anterior pituitary);

3) treatment of non-endocrinic diseases. In these cases, hormonal drugs are used as agents of pathogenetic therapy (e. g., glucocorticoids are used in the treatment for inflammatory diseases);

4) diagnostic tests of functional state of endocrinic glands (e. g., practical use of hypothalamic hormones).

Long-lasting use of hormonal drugs can reduce functional activity of an appropriate gland by the principle of negative feedback. In such case, sudden discontinuation of drug intake can lead to sharp aggravation of the disease or in development of insufficiency of appropriate gland. Therapy with peptide hormones can be accompanied by synthesis of appropriate antibodies.

Hormonal drugs, which obtained from animal glands, undergo biological standardisation. Their activity is given in International Units. Some hormonal drugs are obtained by synthetic and semisynthetic ways; their activity is given in grams.

Drugs of Hypothalamic Hormones

Hypothalamic hormones are devided into releasing factors or liberins (stimulating secretion of appropriate pituitary hormones) and statins (inhibiting secretion of appropriate pituitary hormones).

The following drugs of hypothalamic hormones are used in medicine.

Corticotropin releasing factor (*corticoliberin*) is obtained by synthetic way. The drug stimulates adrenocorticotropin secretion. Corticoliberin is used to make a diagnosis.

Drug of *somatotropin-releasing factor* is called *sermorelin*. The drug stimulates pituitary production of somatotripin. Sermorelin is used to diagnose and treat growth hormone deficiency in children.

Somatostatin is hypothalamic hormone which is also found in peripheral tissues. This hormone inhibits pituitary release of somatotropin, and suppresses the release of glucagone and other

gastrointestinal hormones. Pharmaceutical industry produces synthetic analogue of somatostatin – *octreotide* (*sandostatin*). Indications for use of sandostatin are acromegaly and apudomas (tumors of APUD cells which are located in different tissues and organs, e. g., gastrointestinal tract, central nervous system). The drug is administered subcutaneously.

Another synthetic analogue of somatostatin is called *lanreotide*. This drug is characterised by prolonged action and is administered 1 time in 10–14 days.

Synthetic analogue of *thyrotropin-releasing hormone* (*thyroliberin*) is called *rifothyroin*. The drug stimulates the pituitary secretion of thyrotropin. Rifathyroin is used to diagnose thyroid gland pathology.

Gonadorelin is a synthetic analogue of *gonadotropin-releasing hormone*. It stimulates the release of gonadotropins and is used to treat ovary dysfunction and delayed puberty.

Leuprolide (leuprorelin), buserelin, nafarelin, deslorelin, histrelin, and other drugs are also analogues of *gonadotropin-releasing hormone*. Effects of these drugs depend on the mode of their dosage. If drug is administered with pulsating character (which is similar to natural rhythm of hormone secretion), the stimulative effect develops. A stable long-time concentration of these drugs in the blood reduces pituitary secretion of gonadotropic hormones. Such stable concentrations are used to inhibit gonadotropin secretion (e. g., at treatment of prostate cancer).

Danazol is a synthetic inhibitor of gonadotropin synthesis. The drug causes atrophy of endometrium and inhibits function of ovaries in women and spermatogenesis in men. Danazol is used to treat endometriosis, gynecomastia, and uterine bleeding.

Hormonal Drugs of Anterior Pituitary

Anterior pituitary is a complex of glands, each of which consists of special type of cells. Their secretory activity is under control of appropriate hypothalamic hormones. Anterior pituitary produces the following hormones: adrenocorticotropic hormone (ACTH,

adrenocorticotropin), somatotropin (STH, growth hormone), thyroid-stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

Adrenocorticotropic Hormone

Corticotropin and *tetracosactide* (*synacthen depot, cosyntropin*) are analogues of adrenocorticotropin which used in medicine. Corticotropin is obtained from animal pituitary (cattle, pigs, and sheep). Tetracosactide is a synthetic analogue with prolonged action.

Corticotropin interacts with specific membrane receptors of adrenal cortex cells. Excitation of these receptors is accompanied by activation of adenylyl cyclase that leads to the increase of intracellular cAMP concentration. Due to this, cholesterol is converted into corticosteroids. Corticotropin mainly stimulates the synthesis of glucocorticoids.

Unlike glucocorticoids, short-term use of corticotropin does not inhibit adrenal cortex function. But long-lasting corticotropin's administration leads to exhaustion of adrenal cortex.

Corticotropin stimulates lipolysis and protein catabolism and causes hyperglycemia. Corticotropin reduces the excretion of sodium and increases the excretion of potassium. The drug stimulates gastric secretion. Corticotropin exerts anti-inflammatory, antiallergic, immunosuppressive, and detoxification effects. The drug normalizes tone and permeability of the cerebral vessels, imroves memory, and normalizes the function of the extrapyramidal system.

Corticotropin is administered intramuscularly or intravenously. At intramuscular administration, duration of its action is 6–8 hours. The drug is dosed 4–6 times a day.

There are the following therapeutic indications for corticotropin: hypofunction of adrenal cortex, to diagnose functional ability of adrenal cortex, to prevent glucocorticoid withdrawal syndrome, rheumatism, bronchial asthma, disorders of cerebral circulation, Parkinson disease, and chorea.

Treatment with corticotropin is accompanied by such side effects as oedemas, increased blood pressure, delayed growth or wound healing, insomnia, etc.

Natural corticotropin provokes synthesis of antibodies. Presently, a synthetic analogue with low immunogenic activity, *tetracosactide (Synacthen Depot),* is used in medicine.

Somatotropin (Growth Hormone)

Human growth hormone, *somatotropin*, nowardays is produced by genetic engineering. *Somatrem* is a synthetic analogue of somatotropin.

Somatotropin stimulates growth of bones and internal organs and increases the body weight. Growth hormone stimulates the synthesis of proteins and RNA; increases the transport of amino acids into the cells; retards in a body phosphorus, calcium, and sodium; causes hyperglycemia and lipolysis.

Somatotropin is administered subcutaneously or intramuscularly. The period of its half-life is 4–5 minutes. About 90 % administered dose is metabolized in the liver. Course of treatment lasts from 3 months to 2 years.

Somatotropin is used to treat nanism in children and osteoporosis in adults.

Side effects of somatotropin include allergic reactions, anorexia, headache, irritability, etc. The drug is contraindicated at neoplasma.

Somatostatin is hypothalamic hormone which has been synthesized. This hormone inhibits the release of somatotropin by pituitary. Synthetic somatostatin may be used to treat gigantism and acromegaly. But practically, the drug is unuseful due to very short duration of action (half-life period is 3–6 minutes).

Sandostatin is a synthetic octapeptide – analogue of somatostatin, with longer duration of action (half-life period is 100 minutes). The drug is administered subcutaneously 2–3 times a day. *Octreotide (Sandostatin LAR)* and *lanreotide (Somatuline® Depot Injection)* are drugs which act longer than sandostatin. Octreotide is dosed intramuscularly once per 4 weeks.

Lanreotide is administered subcutaneously or intramuscularly 1 time in 10–14 days. Therapeutic indications for these drugs are the follows: acromegaly, symptomatic treatment of endocrine tumors of gastrointestinal tract and pancreas, prevention of complications after surgery on the pancreas, acute pancreatitis, and persistent diarrhea in AIDS patients.

Besides, dopaminomimetic *bromocriptine* is used to treat acromegaly.

Thyrotropin

Thyrotropin stimulates the secretion of thyroid hormones. Drug is obtained from bovine anterior pituitary. Thyrotropin interacts with specific receptors of the cells of thyroid gland and activates adenylyl cyclase. It results in the increase of intracellular concentration of cAMP. Thyrotropin activates the uptake of iodine by thyroid gland, iodination of tyrosine, synthesis of thyroid hormones, and their releasing into blood. Besides, thyrotropin activates the metabolism of carbohydrates, lipids, and proteins.

Thyrotropin is administered subcutaneously and intramuscularly. The drug is used for differential diagnostics of myxoedema. Sometimes, drug is used in the treatment for thyroid malignant tumors. In this case, thyrotropin is administered together with radioactive iodine.

Follicle-Stimulating Hormone

Follicle-stimulating hormone does not exert sex specificity. The hormone stimulates the development of follicules and estrogen synthesis in women and the development of seminiferous tubules and spermatogenesis in men.

Human menopausal gonadotropin (*HMG*) is preparation of follicle-stimulating hormone which is obtained from the urine of postmenopausal women. The drug is used in the treatent for infertility in women for stimulation of ovarian follicle development and estrogen synthesis. HMG is also used in the treatment for sexual infantilism, cryptorchidism, and hypogonadism of hypothalamic-

pituitary origin in men. Human menopausal gonadotropin is administered intramuscularly. Both in women and in men, the drug should be used in combination with luteinizing hormone. Side effects of HMG are allergic reactions, excessive increase in the ovary size, and abdominal pain.

Luteinizing Hormone

Luteinizing hormone does not exert sex specificity. In women, hormone stimulates ovulation, transformation of follicles into corpus luteum, and generation and release of progesterone and estrogens. In men, luteinizing hormone stimulates development of testicular Leydig cells and testosterone synthesis.

Human chorionic gonadotropin (*HCG*) is therapeutic preparation of luteinizing hormone. The drug is obtained from urine of pregnant women (HCG is produced by placenta). The drug is prescribed for woman with disorders of menstrual cycle and to treat infertility. In man, the drug is used to treat sexual infantilism and cryptorchism. Sometimes, HCG is used in the treatment for benign breast tumors, endometritis, gynecomastia, and uterine bleeding. Human chorionic gonadotropin is administered intramuscularly. Its side effects are allergic reactions and excessive increase of the ovary size or testicles.

Prolactin

Prolactin stimulates mammary gland development and lactation. Therapeutic preparation of prolactin is obtained from pituitary of bovine. Prolactin is used to stimulate lactation in women in postpartum period. The drug is administered intramuscularly. Prolactin is contraindicated in women with a tendency to allergy.

Bromocriptine is adrenomimetic agent inhibiting prolactin synthesis by anterior pituitary. The drug is used in the treatment for patients with symptomatic hyperprolactinemia. Besides, acromegaly and Parkinson’s disease are also therapeutic indications for bromocriptine.

Melanocyte-Stimulating Hormones

Melanocyte-stimulating hormones are synthesized by intermediate lobe of pituitary. These hormones increase the sensitivity of retinal cells that results in improving visual acuity and dark adaptation. *Intermedin* is a therapeutic preparation of melanocyte-stimulating hormones. The drug is obtained from bovine pituitary. Intermedin is used in the treatment for day blindness and retinal degenerative changes. The drug is instilled into the conjunctival cavity. Sometimes, intermedin is administered as subconjunctival injections and by means of electrophoresis.

Hormonal Drugs of Posterior Pituitary

Posterior pituitary (or neurohypophisis) consists of axons of cells extending from the supraoptic and paraventricular nuclei of hypothalamus. These axons release into blood hormones oxytocin and vasopressin. Both these hormones are polypeptides.

Oxytocin stimulates the uterine contraction and relaxes uterine neck. The uterus in the last period of pregnancy is especially sensitive to oxytocin. It is due to activity of estrogens preparing uterus to delivery. In uterus, estrogens promote accumulation of ATP, glycogen, potassium, calcium, magnesium, acetylcholine, etc. The high sensitivity of uterus to oxytocin persists during several days after delivery. Besides, oxytocin influences the alveoli cells of mammary gland and stimulates lactation.

Oxytocin is used to stimulate delivery, to arrest uterine bleeding in postpartum or postabortion periods, and to stimulate lactation. Drug is administered intramuscularly, intravenously, and in the uterus neck.

Desaminooxytocin (demoxytocin) is a synthetic analogue of oxytocin with longer duration of action. The drug is manufactured in tablets for buccal use. Demoxytocin are used to accelerate uterine involution (reduction of the uterine body size) in the postpartum period and to stimulate lactation.

Vasopressin (antidiuretic hormone) promotes water retention in organism and stimulates smooth muscles of the internal organs.

The main function of the hormone is stimulation of water reabsorption in distal segment of nephron and in collecting ducts. Vasopressin influence upon smooth muscles is observed only if high doses of drug are used. In this case, the drug increases smooth muscle tone of arterioles, capillaries, intestine, and uterus. But vasopressin relaxes bronchi and facilitates lactation. Besides, vasopressin stimulates the platelet aggregation, increases concentration of VII factor of blood clotting, and promotes the secretion of adrenocorticotropin by anterior pituitary.

The following vasopressin preparations are used in medicine: *vasopressin, pituitrin, adiuretin, desmopressin,* and *felypressin*. Vasopressin is administered subcutaneously or intramuscularly and acts 0.5–2 hours. Adiuretin and desmopressin exert more expressed antidiuretic effect. These drugs are applied intranasally by nasal drops (1–4 drops every 12 hours) or, sometimes, parenterally (subcutaneously, intramuscularly, or intravenously). The main therapeutic indication for vasopressin preparations is diabetes insipidus. Besides, these drugs are used in the treatment for acute arterial hypotension, intestinal atony, and bleeding from esophageal varices in patients with cirrhosis.

Hormonal Drugs of Epiphysis

Epiphysis synthesizes several peptide hormones, the main of which is melatonin (tryptophan derivative). This hormone regulates circadian rhythms of human body. Highest level of melatonin secretion is observed during night. Melatonin synthesis elevates when excitation of retina by light is decreased. Besides, hormone regulates seasonal sex activity. Melatonin exerts moderat hypnotic effect and decreases body temperature and secretion of luteinizing hormone. Also, melatonin exhibits immunostimulatory and antioxidative effects.

Three types of melatonin receptors are found out in human body: Mel_{1A}, Mel_{1B}, and Mel_{1C}. These receptors are located in suprachiasmatic nuclei of the hypothalamus, retina, some nuclei of

thalamus and anterior hypothalamic region, sex glands, and limphocytes.

Melatonin preparation *Melaxen* is used to treat insomnia and to regulate circadian rhythm for person adaptation at fast change of time zone. The drug is dosed 0.001–0.005 g orally or sublingually at evening. Melaxen is readily absorbed from gastrointestinal tract, easily penetrate central nervous system, and is quickly metabolized. Its side effects are drowsiness and mild oedemas.

Thyroid and Antithyroid Drugs

Thyroid gland synthesizes and releases iodine-containing hormones triiodothyronine (T_3) and tetraiodothyronine (thyroxine, T_4) and polypeptide hormone calcitonin. The last hormone participates in regulation of calcium metabolism. Circulated in blood iodine ions are absorbed by thyroid gland where they are oxidized to iodine. Molecular iodine interacts with tyrosine forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). This process is called iodine organification. MIT and DIT produce triiodothyrosine and thyroxine. Thyroid hormones are accumulated in the follicles of the thyroid gland in form of thyroglobulin.

Hypothalamic hormone thyroliberin regulates the secretion of thyrotropin by anterior pituitary. Thyrotropin stimulates the synthesis of thyroglobulin. In turn, there is negative feedback inhibition of the synthesis of appropriate hypothalamic and pituitary hormones by means of thyroid hormones circulating in blood.

Thyroid Hormones

Thyroid hormones influence the permeability of mitochondrial membranes and stimulate mitochondrial electron transport. It is accompanied by the increase of oxygen consumption, basal metabolism, and body temperature. Thyroid hormones stimulate catabolism of carbohydrates and lipids and decrease the level of cholesterol. Thyroid hormones regulate the synthesis of RNA, stimulate the activity of some cellular enzymes and growth and development of body.

The hormones increase intracellular concentration of cAMP due to stimulation of adenylyl cyclase. It is accompanied by the increase of heart rate, stroke volume, cardiac output, and blood pressure. Thyroid hormones potentiate the effects of catecholamines.

Thyroid deficiency in children leads to cretinism (mental retardation and dwarfism). Hypofunction of thyroid gland in adults causes myxedema (slowdown of metabolism, reduced mental and physical performance, apathy, mucous oedema of tissues, weight gain, etc.).

Thyroid hyperfunction results in hyperthyroidism or thyrotoxicosis (acceleration of metabolism, increased activity of sympathetic nervous system, tachycardia, cardiac arrhythmias, nervousness, etc.).

Thyroid preparations include drugs of synthetic origin *L-thyroxine* and *triiodothyronine hydrochloride (liothyronine)* and the drug of animal origin – *thyreoidine*. There are coformulated drugs of thyroid hormones, e. g., *Thyreocomb* (contains levothyroxine, liothyronine, and potassium iodide), *Thyreotom* (contains levothyroxine sodium and liothyronine), etc.

Thyroidine is obtained from desiccated and defatted thyroid gland of bovine. The drug contains a mix of thyroid hormones and is characterised by unstable activity. Thyroidine is taken orally in 30 minutes before a meal. Onset of action develops in 2–3 days. Duration of its action is 3–4 weeks.

L-thyroxine is taken orally and, sometimes, administered intravenously. Its effect develops gradually. The maximum is observed in 8–10 days. Duration of its effect is several weeks.

Maximal effect of *triiodothyronine* is observed in 24–48 hours after intake. Duration of its action is several days. In comparison to thyroxine, triiodothyronine exhibits 3–5 times higher influence upon metabolism. The drug is taken orally.

The drugs of thyroid hormones are used for substitutive therapy in patients suffering from cretinism and myxedema. Besides these forms of hypothyroidism, the development of hypothyroid coma also

is possible. This patological state is characterized by the development of cardiovascular failure, dry and cold skin, oedemas of serosal and mucosal membranes. Treatment of hypothyroid coma is the following: immediate intravenous administration of 50 mg thyroxine, which should be repeated every 6–12 hours. Intravenous administration of a daily dose of thyroxine 100 mg is used for 10 days. Subsequent treatment is based on oral intake of the hormone.

In patients with hypothyroidism caused by iodine deficiency in the diet, the treatment is based on the enrichment of diet by iodine (iodinated salt, iodine rich foods).

Antithyroid Drugs

In comparison to hypothyroidism, hyperthyroidism is more common clinical pathology. The main manifestations of hyperthyroidism are the following: toxic goiter, tachycardia, nervousness, tremor, weight loss, low tolerance to heat, etc. At hyperthyroidism, level of basal metabolism increases by 20–60 %.

The following groups of drugs are used to treat hyperthyroidism:

1) drugs inhibiting the thyreotropin synthesis by anterior pituitary: *potassium iodide, iodine solution;*

2) drugs which inhibit synthesis of thyroid hormones by thyroid gland: *mercazolil, propylthiouracil;*

3) drugs affecting iodine uptake by thyroid gland: *potassium perchlorate;*

4) drugs which destroy follicular cells of the thyroid gland: *radioactive iodine*.

Iodine-containing drugs *potassium iodide* and *iodine solution* are prescribed in high doses (daily dose is more than 6 mg). In this case, these drugs inhibit thyrotropin synthesis by anterior pituitary that results in reduction of thyroid hormone synthesis and their release in blood. Both size and vascularization of thyroid gland are decreased. Antithyroid effect of iodine-containing drugs is moderate and unstable. These agents are used only at mild form of thyrotoxicosis or to prepare patients for surgery. Side effects

of iodine-containing drugs are acne, hypersecretion of bronchial glands, metallic taste in the mouth, nausea, vomiting, etc.

Mechanism of action of *mercazolil* and *propylthiouracil* is associated with inhibition of synthesis of triiodothyronines and thyroxine. These drugs inhibit thyroid peroxidase – enzyme oxidizing iodine into active form and promoting iodination of tyrosine and synthesis of thyroid hormones. Besides, propylthiouracil inhibits transformation of thyroxine into triiodothyronine. Both drugs are taken orally. Therapy with these drugs results in reduction of thyrotoxicosis. But the size of the thyroid gland increases (goitrogenic effect). Goitrogenic effect is caused by the fact that the anterior pituitary increases the secretion of thyrotropin. Other side effects of mercazolil and propylthiouracil include leukopenia and agranulocytosis. Therefore, the constant monitoring of blood is required.

Potassium perchlorate reduces active uptake of iodine by thyroid gland. The drug is used mainly to treat mild and moderate forms of thyrotoxicosis in cases when other drugs are ineffective. Therapy with potassium perchlorate can provoke aplastic anemia.

Sometimes, *radioactive iodine* (^{131}I and ^{132}I) is used to treat hyperthyroidism. Half-life of ^{131}I is 8 days, and half-life of ^{132}I is 2–3 hours. Destruction of thyroid gland cells develops due to the influence of β- and γ-rays. Drugs containing radioactive iodine are dosed orally. Their effect develops in 1–3 months after start of the drug intake.

Calcitonin

Calcitonin is a polypeptide hormone secreted by parafollicular cells (C cells) of thyroid gland. Calcitonin regulates calcium-phosphate metabolism. The hormone inhibits decalcification of bones and decreases calcium concentration in the blood. Calcitonin does not influence intestinal absorption of calcium and renal calcium excretion. There are synthetic analogues of calcitonin – *Cibacalcin*, *Miacalcic*, and *Calcitrin*. These drugs are used to treat osteoporosis and nephrocalcinosis.

Hormonal Drugs of Parathyroid Glands

Parathyroid glands secrete *parathyroidin*. It is a polypeptide which consists of 84 amino acids. The main function of parathyroidin is to regulate calcium and phosphorus metabolism. The hormone stimulates decalcification of bones and increases calcium concentration in blood. Besides, parathyroidin promotes intestinal absorption of calcium and reabsorption of calcium in renal tubules. Simulateneously, parathyroidin inhibits renal reabsorption of phosphorus that results in the reduced concentration of phosphorus in blood.

For therapeutic use, parathyroidin is obtained from the parathyroid glands of cattle. Its effect develops in 4 hours after administration. Duration of action is about 1 day. Parathyroidin is used in the treatment for chronic hypoparathyroidism and spasmophilia. The drug is administered subcutaneously and intramuscularly. It should be noticed that at acute hypoparathyroidism (tetany), calcium chloride or calcium gluconate are administered intravenously together with parathyroidin. At these states, the hormone is not administered alone due to the long latency period.

Since 2002, a recombinant form of parathyroid hormone consisting of the 34 amino acids is used in medicine – *teriparatide (Forteo).*

Hormonal Drugs of Pancreas

Antidiabetic Drugs

The endocrine part of pancreas (it is about 1 islets of Langerhans) consists mainly of β-cells (about 60–80 %) producing insulin. Besides β-cells, pancreas contains α-cells producing glucagon and σ-cells secreting somatostatin. There are also F-cells producing pancreatic polypeptide activating digestion. Main pancreatic hormones, insulin and glucagon, support the blood glucose concentration within normal physiological range. Disorders of these gormons secretion may provoke hyperglycemia or hypoglycemia.

Insulin is most valuable pancreatic hormone for practical medicine, because it is used to treat diabetes mellitus. Diabetes mellitus is metabolic disorders which characterized by high glucose blood level, glucosuria, accumulation of ketone bodies in the blood with following acidosis and intoxication; damage of capillaries in kidneys, retina, and nervous system; generalizing atherosclerosis, etc. Protein catabolism is increased, and amino acids is converted to glucose due to hepatic gluconeogenesis. Catabolism of lipids and fatty acids is also accelerated that leads to formation of ketone bodies. Renal excretion of glucose, nitrogenous substances, and ketone bodies promote osmotic diuresis that leads to dehydration and disorders of electrolyte and acid-base balance. According to WHO, this disease affects approximately from 0.8 % to 8 % of the population in different world countries and exerts tendency to increase.

There are two types of diabetes mellitus: insulin-dependent diabetes mellitus (type I) and non-insulin-dependent diabetes mellitus (type II).

Type I diabetes mellitus develops due to autoimmune destruction of pancreatic β-cells. About 10 % of diabetic patients are suffering from this type of disease. Type II of diabetes mellitus involves multiple factors for genetic predisposition to the disease. Frequency of type II diabetes is about 90 % diabetic patients.

In severe cases of type I diabetes mellitus, diabetic ketoacidosis, serious complication of type I diabetes, occurs. Type II diabetes may be aggravated by hyperosmolar coma with hyperglycemia and dehydration.

Antidiabetic drugs are classified as follows.

1. Drugs for substitutive therapy: insulin prepartions.

2. Synthetic antidiabetic drugs (oral hypoglycemic drugs).

2.1. Sulfonylurea derivatives:

– first-generation sulfonylureas: *acetohexamide, chlorpropamide, tolazamide,* and *tolbutamide;*

– second-generation sulfonylureas: *glibenclamide* and *glipizide;*

– third-generation sulfonylureas: *glimepiride*.

2.2. Biguanides: *metformin* and *buformin*.

2.3. Thiazolidinediones: *rosiglitazone* and *pioglitazone*.

2.4. α-Glucosidase inhibitors: *acarbose* and *miglitol*.

Insulin Preparations

Insulin is most effective antidiabetic drug. It is a protein consisting of 51 amino acids, which are arranged in two polypeptide chains, an α-chain containing 21 amino acids and β-chain containing 30 amino acids. Chains are linked by means of two disulfide bonds.

Pancreatic secretion of insulin depends on glucose level. Glucose penetrates β-cells and undergoes metabolism that provides the increase of intracellular ATP. ATP blocks ATP-dependent potassium channels that leads to depolarization of cellular membranes. It increases calcium entrance into β-cells through potential-dependent calcium channels and following secretion of insulin. Besides glucose, amino acids, free fatty acids, glycogen, secretin, electrolytes, and parasympathetic nervous system are factors stimulating insulin secretion.

Mechanism of insulin action is not clear enough. Insulin binds with specific receptors which are located in the cellular membranes of most tissues. A primary target tissues for insulin are liver, muscle, and adipose tissue. Insulin receptor consists of two parts, each of which consists of α-subunit (it is locolated extracellularly and is a recognition site) and β-subunit spanning cellular membrane. The β-subunit contains a tyrosine kinase. The binding of insulin with the α-subunits leads to conformational change which brings the catalytic loops of β-subunits into closer proximity. Tyrosine kinase is phosphorylated that leads to activation of some second intracellular messengers with development of multiple metabolic effects.

Effects of insulin are complex and involve changes in carbohydrate, protein, and lipid metabolism. Insulin activates glucose transport through cellular membranes and its utilization by peripheral tissues.

Additionally to its role in stimulation of glucose uptake by tissues, insulin exerts the following effects:

– reduction of glycogenolysis in liver and in skeletal muscles due to glycogen phosphorylase inhibition;

– activation of glycogen synthesis owing to stimulation of glycogen synthetase;

– inhibition of gluconeogenesis (transformation of noncarbohydrate substrates, like amino acids, into glucose);

– reduction of lipolysis due to inhibition of lipase activity that leads to the decrease of concentration of free fatty acids and glycerol in plasma and elimination of ketoacidosis (blood concentration of acetone, acetoacetic and hydroxy-butyric acids is reduced);

– activation of transport of amino acids into cells and stimulation of protein synthesis that results in positive nitrogen balance.

Thus, blood concentration of glucose is reduced and glucosuria, polyuria, and thirst are disappeared. Normalization of protein metabolism is accompanied by activation of anabolic processes in the body and reduction of concentration of nitrogen compounds in urine. Body weight loss is terminated.

Insulin preparations are dosed by International Units (IU). Preparations are tested on hungry rabbits. One International Unit of insulin is amount of hormone which reduces glucose in the rabbit's blood in 45 mg %.

Insulin preparations are classified on the base of their duration of action as follows.

1. Rapid-acting insulin analogues: *insulin lispro (Humalog), insulin glulisine (Apidra),* and *insulin Aspart (NovoLog)*. Their onset of action is within several minutes, duration of action is about 5 hours.

2. Short-acting insulins: *Actrapid, Humulin R, Novolin R*. Their onset of action is in 30 minutes after administration, duration – 6–8 hours.

3. Intermediate-acting insulins.

3.1. Monocomponent drugs: *Monotard HM, Protaphane HM, Humulin L (Lente), isophane insulin suspension*.

Their onset of effect is in 1.5–2 hours, duration of action – 16–24 hours.

3.2. Premixed insulins (containing short-acting and intermediate-acting insulins): *Humulin M2, Humulin M3, Novolin 70/30* (mixture of 70 % intermediate-acting insulin and 30 % short-acting insulin).

4. Long-acting insulins: *Ultralente Insulin (extended insulin Zinc suspension), Ultratard HM, insulin glargine (Lantus), insulin detemir (Levemir), and insulin degludec (Tresiba)*. Their onset of action is about 4 hours, duration of action up to 36 hours and more (up to 42 hours – for Tresiba).

Insulin is most commonly administered subcutaneously. Intramuscular injections of insulin are used less often because of more rapid absorption. Insulin is a polypeptide hormone; therefore, it is readily inactivated if administered orally. In emergencies, such as severe diabetic ketoacidosis, insulin is dosed intravenously. Plasma half-life of insulin is less than 10 minutes. A liver and kidneys are the main organs of hormone uptake and degradation. Hepatic insulinase inactivates about 50 % circulating insulin.

Animal (beef and pork) insulins were the first insulin preparations which been introduced in clinical practice. Beef insulin differs from human insulin by three amino acids, whereas only one amino acid is different in human insulin and porcine. Therefore, beef insulin was slightly more antigenic than pork insulin.

Presently, production of human insulin is carried out by means of recombinant DNA techniques. For this aim, human proinsulin gene is inserted into Escherichia coli or yeast. Extracted proinsulin undergoes further processing to obtain a molecule of human insulin.

Rapid-acting insulins and short-acting insulins are clear solutions with neutral pH containing small amounts of zinc to improve their stability. Intermediate-acting and long-acting insulins are suspensions (except long-acting insulin analogues) containing either protamine or different zinc concentrations.

Insulin analogues are obtained by means of chemical modification of human insulin molecules. Thus, *insulin lispro*

(Humalog) is produced by replacement of the positions of lysine-proline residues in the β-chain of insulin molecule. Due to this chemical change, insulin lispro cannot form stable hexamers or dimers in subcutaneous tissue that promotes its rapid absorption and onset of action.

Short-acting insulins *(Humulin R, Novolin R, etc.)* are also called regular insulins. Their onset of action is about 30 minutes. These drugs have a longer duration of action than rapid-acting insulin analogues. Regular insulins are administered in 30 minutes before a meal. Short-acting insulins are used to supplement intermediate- and long-acting insulin preparations. Also, these insulins are the drugs of choice for control of glucose concentration in blood during surgery, trauma, and shock. At hyperglycemic coma, short-acting insulin is administered intravenously.

Intermediate-acting insulins are *NPH insulin (isophane insulin suspension)*, *insulin Lente (insulin zinc suspension)*, etc. These drugs have a slower onset of action (1–2 hours). Duration of their action is longer (about 13–24 hours) due to conjugation of insulin molecules with either zinc ions or protamine. These drugs are administered 1–2 times a day.

Some preparations of intermediate-acting insulins are combinations with short-acting insulins in premixed ratio: 70 : 30, 50 : 50, etc.

Protamine zinc insulin and *insulin Ultralente* are representatives of long-acting insulin preparations. In contrast with intermediate-acting insulins, these drugs have more protamine and zinc in the mixture. Their onset of action 2–4 hours and duration of action about 36 hours.

Insulin glargine (Lantus), insulin detemir (Levemir), and insulin degludec (Tresiba) are long-acting insulin analogues. Glargine is soluble in manufactured acidic solution but precipitates in the more neutral body pH after subcutaneous injection. Glargine has a slow onset (1–2 hours) and long duration (up to 24 hours) of action. The drug is administered 1 time a day.

The main therapeutic indication for insulin is to treat type I diabetes mellites. Insulin is also used in the treatment for type II diabetes in patients which are refractory to oral hypoglycemic drugs. As a rule, insulin is administered as subcutaneous injection by means of needles and syringes. Portable pen injectors containing cartridges of insulin and replaceable needles are also widely used. Nowadays, insulin pumps are used in practice. Insulin pump contains an insulin reservoir, programme chip, keypad, and display screen. Insulin pump is usually placed on the abdomen. The insulin reservoir, tubing, and infusion set need to be changed every 2 or 3 days.

The most common side effect of insulin is hypoglycemia which is manifested by tremors, lethargy, hunger, confusion, motor and sensory deficits, convulsions, anxiety, palpitations, tachycardia, and unconsciousness. In many cases, oral intake of carbohydrates (e. g., fruit juice, candys, or glucose tablets) can restore normal glucose blood level. At hypoglycemic coma, intravenous glucose, subcutaneous or intramuscular adrenaline, or intramuscular glucagon are administered.

Another frequent side effect of insulin therapy is weight gain.

Allergic reactions due to the use of recombinant DNA-derived human insulins are seldom. Local lipodystrophy (lipohypertrophy or lipoatrophy) due to repeated subcutaneous injections of human insulin is very seldom complication. Hypokalemia is possible due to the stimulation of Na^+, K^+-ATPase with redistribution of K^+ ions intracellularly. This property of insulin is sometimes used in the emergency treatment of hyperkalemia.

Oral Hypoglycemic Drugs

Since 1955, synthetic oral hypoglycemic drugs are used to treat II type diabetes mellitus. These drugs are classified as follows.

1. Sulfonylurea derivatives.

1.1. First-generation sulfonylureas: *acetohexamide, chlorpropamide, tolazamide, tolbutamide*.

1.2. Second-generation sulfonylureas: *glibenclamide (Maninil), glipizide*.

1.3. Third-generation sulfonylureas: *glimepiride*.
2. Biguanides: *metformin (Gliformin)*.
3. Thiazolidinediones: *rosiglitazone* and *pioglitazone*.
4. α-Glucosidase inhibitors: *acarbose*, and *miglitol*.

Sulfonylurea Derivatives

Sulfonylurea derivatives are the most widely used drugs to treat type II diabetes mellitus.

Nowadays, the drugs of first-generation are not frequently used in the treatment of diabetes mellitus, because these drugs have relatively low specificity of action, slow onset of action, and many side effects.

The second-generation and third-generation sulfonylurea derivatives are characterized by a higher specificity and affinity for the sulfonylurea receptor, more predictable pharmacokinetics, and relatively fewer side effects. These drugs may also exert mild diuretic effects.

The mechanism of action of the sulfonylurea derivatives is associated with stimulation of insulin release due to interaction with sulfonylurea receptors of pancreatic β-cells. Sulfonylurea receptor is an ATP-sensitive potassium channel that is located on the β-cell membrane. A blockage of these channels by sulfonylurea derivatives leads to depolarization of β-cell membrane and opening of voltage-dependent calcium channels. Calcium ions entrance in β-cell results in insulin release. Simultaneously, sensitivity of β-cells to glucose and amino acids is increased that also promotes insulin secretion. Therapy by sulfonylurea derivatives is accompanied by the increase of quantity of insulin receptors on the target cells.

Besides, sulfonylurea derivatives decrease glucagon secretion by pancreatic α-cells. The higher doses of sulfonylurea derivatives also decrease hepatic production of glucose.

Additionally, II- and III-generation drugs exert cholesterol lowering and antiaggregant effects and improve tissue microcirculation.

Sulfonylurea derivatives are taken orally. Drugs are characterized by high degree of binding with plasma proteins and undergo hepatic metabolism by microsomal enzymes.

Sulfonylurea derivatives are used to treat mild and moderate diabetes mellitus of type II. These drugs are ineffective in patients with type I diabetes mellitus.

Side effects of sulfonylurea derivatives are dispepsy, hypoglycemia, weight gain, fluid retention, oedemas, leukopenia, allergic reactions, cholestatic jaundice, and decreased alcohol tolerance (disulfiram-like effect).

Nateglinide (Starlix) is D-phenylalanine derivative exerting similar mechanism of action with sulfonylurea derivatives. Nateglinide and sulfonylurea derivatives are commonly included into the group of so-called "insulin secretagogues". Nateglinide is taken before a meal to regulate postprandial (postalimentary) glycemia. The drug has high gastrointestinal bioavailability, short duration of action (its half-life is 1.5 hours) and fast onset of effect. Nateglinide is well tolerated by patients. Hypoglycemia is observed seldom.

It is known that at food intake, small bowel releases two hormones: glucose-dependent insulinotropic peptide (gastroinhibitory peptide, GIP) and glucagon-like peptide-1 (GLP-1). *Exenatide (Byetta)* is analogue of GLP-1 which is intended to treat II type diabetes mellitus. The drug amplifies insulin secretion stimulated by glucose. Exenatide is dosed subcutaneously 2 times a day. A main route of its excretion is kidneys. Side effects of exenatide are nausea, vomiting, diarrhea, and hypoglycemia.

Biguanides

Biguanides are hypoglycemic agents which are used for oral intake. The mechanism of action of biguanides is associated with their ability to stimulate glycolysis in tissues that leads to reduction of blood glucose level. Besides, biguanides suppress hepatic and renal gluconeogenesis. Also, the drugs reduce the gastrointestinal glucose absorption and decrease glucagon level in plasma.

The main representative of this group is *metformin*. The drug exerts antiatherosclerotic (decreases level of atherogenic lipoproteins) and antiaggregant effects and improve tissue microcirculation. Also, metformin inhibits appetite and promotes decrease of body weight.

Metformin is used in the treatment of II type of diabetes mellitus, especially against the background of obesity. The drug is taken orally 2–3 times a day at mealtimes. Hypoglycemia is uncharacteristic of metformin therapy. Common side effects of metformin are nausea, vomiting, anorexia, metallic taste, and diarrhea. Also, the drug can cause lactic acidosis and decrases cyanocobalamin absorption. Metformin is contraindicated in patients with hepatic dysfunction.

Thiazolidinediones

Rosiglitazone and *pioglitazone* are thiazolidinedione derivatives which sensitize cells to insulin. Thiazolidinediones reduce insulin resistance and increase insulin action in target tissues due to activation of nuclear peroxisome proliferator-activated receptors (PPAR). These receptors are located in adipose tissue, muscle, and liver and modulate the expression of genes involving in insulin signal transduction and lipid and glucose metabolism. Thus, thiazolidinediones increase utilization of glucose and fatty acids by tissues and inhibit gluconeogenesis.

Thiazolidinediones are used in the treatment for II type of diabetes mellitus. Their side effects are edema, weight gain, and mild anemia. Thiazolidinediones are contraindicated in severe heart failure.

α-Glucosidase Inhibitors

Representatives of α-glucosidase inhibitors are *acarbose* and *miglitol*. α-Glucosidase inhibitors decrease postprandial hyperglycemia by slowing down of gastrointestinal carbohydrate absorbtion. These drugs competitively inhibit intestinal α-glucosidases (glucoamylase, sucrase, maltase, and dextranase).

α-Glucosidase inhibitors are taken before meal or at mealtimes to treat type II diabetes mellitus. As a rule, acarbose is not used alone. Commonly, this drug is prescribed together with insulin or sulfonylurea derivatives. Combination with metformin is unreasonable because acarbose reduces metformin absorption. Most common side effect of α-glucosidase inhibitors is flatulence (observed in 20–30 % patients).

Glucagon

Glucagon is synthesized by pancreatic α-cells. It is a peptide consisting of 29 amino acids. Glucagon binds to specific receptors of hepatocytes which are coupled with G_s-proteins. This increases adenylyl cyclase activity and intracellular cAMP concentration. It results in the suppression of glycogen synthase and activation of glycogen phosphorylase with following intensification of glycogenolysis, gluconeogenesis and ketogenesis. Thus, glucose concentration in the blood is increased.

Glucagon exerts positive inotropic, chronotropic, and dromotropic effects. These effects are associated with activation of calcium ions uptake by sarcoplasmic reticulum of cardiac histiocytes and accumulation of ATP in myocardium. Besides, glucagon promotes epinephrine release from adrenal medulla and stimulates secretion of somatotropin and calcitonin.

Glucagon is dosed subcutaneously or intravenously in emergency treatment for hypoglycemic coma, heart failure, and cardiogenic shock. Also, glucagon may be used to reverse cardiac effects of β-adrenergic antagonists at their overdose. It should be noticed that glucagon increases oxygen demand of myocardium.

Glucagon undergoes fast enzymatic inactivation in liver, kidneys, blood, and other tissues. Its half-life is about 3–6 minutes.

Table 11 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Corticotropinum	Intramuscularly 10–20 IU 3–4 times a day	Vials containing 10; 20; 30 or 40I A of powder for injection
Oxytocinum	Intravenously drop-by-drop 5 IU in 500 ml of isotonic glucose solution; intramuscularly 0.2–2 IU	Ampoules 1 or 2 ml (5 IU in 1 ml)
Adiuretinum SD	Into nose 1–4 drops 2–3 times a day	Vials 5 ml of 0.01 % solution
Triiodthyronini hydrochloridum	Orally 0.000 02–0.000 05 g daily (in 1–3 intakes)	Tablets 0.000 02 or 0.000 05 g
Mercazolilum	Orally 0.005 g 3–4 times daily	Tablets 0.005 g
Actrapid HM	Subcutaneously – dose is chosen individually, as a rule 7–20 IU 3 times a day in 30 minutes before a meal	Vials 10 ml (in 1 ml – 100 IU of short-acting insulin)
Susp. Protaphane HM	Subcutaneously – dose is chosen individually, as a rule 0.3–1.0 IU/kg/daily (daily dose is divided in 2 administrations)	Vials 10 ml (in 1 ml – 100 IU of intermediate-acting insulin)
Insulin glargine	Subcutaneously 1 time a day in individually chosen dose	Cartridges 3 ml (in 1 ml – 100 IU of insulin glargine); vials 10 ml (in 1 ml – 100 IU)
Glibenclamidum	Orally 0.002 5–0.05 g 1 time a day (before breakfast)	Tablets 0.005 g
Metforminum	Orally 0.5 g 2–3 times a day (at mealtimes)	Tablets 0.5 g

Hormonal Drugs of Adrenal Cortex

Hormones of adrenal cortex are devided into 3 groups:

1) glucocorticoids: hydrocortisone and corticosterone;
2) mineralocorticoids: aldosterone and desoxycorticosterone;
3) sex hormones: androgens, estrogens and progestins.

Glucocorticoids

The main function of glucocorticoids is to provide body resistance to different extremal influences. Glucocorticoids provide "the second" line of body protection, while hormones of adrenal medulla (epinephrine and norepinephrine) participate in "the first" (immediate) line of protection. Maximal secretion of glucocorticoids is observed about 8 a.m. while minimal – in the middle of night. Glucocorticoids secretion increases up to the age of 30, then it reduces gradually. Glucocorticoid concentration is higher in males.

Cortisone and *hydrocortisone* are natural glucocorticoids which preparations are used in medicine. Their synthetic analogues *prednisolone* and *prednisone* have more wide practical use. Due to double bond between C_1 and C_2 atoms of steroid ring in molecules, an anti-inflammatory activity of these synthetic agents is 3–5 times higher than the activity of natural hormones.

Glucocorticoid activity increases even more due to inclusion of fluorine atoms in molecular structure of a drug. *Triamcinolone* and *dexamethasone* contein one fluorine atom in a molecule that increases their anti-inflammatory activity 5–30 times respectively in contrast to cortisone. Besides, these drugs have almost no mineralocorticoid activity.

Sinaflan and *flumethasone* contain two fluorine atoms and have still higher anti-inflammatory activity. These drugs are not permeable through biomembranes and are used only topically as ointments and creams.

Beclomethasone and *fluticasone* are glucocorticoids which do not exert systemic action; these drugs are used as inhalations.

According to their duration of action, glucocorticoids are classified as follows.

1. Glucocorticoid preparations with short duration of action (5–12 hours): *cortisone, hydrocortisone*.

2. Glucocorticoid preparations with intermediate duration of action (12–30 hours): *prednisolone,methylprednisolone,* and *prednisone.*

3. Glucocorticoid preparations with long duration of action (36–72 hours): *triamcinolone, dexamethasone, beclomethasone* and *fluticasone*.

Mechanism of action of glucocorticoids is the follows. Glucocorticoids bind with cytoplasmic receptors of target tissue cells. Complex steroid receptor penetrates nucleus and binds with DNA. It leads to activation of certain genes' transcription with the following increase of activity of some enzymes (mainly catabolic) and decrease of activity of other enzymes (mainly anabolic). It results in changes of metabolism which are typical for glucocrticoids.

Carbohydrate metabolism. Glucocorticoids stimulate hepatic gluconeogenesis, reduce glucose utilization by fat tissue, and increase glucose blood level. Simultaneously, hormones stimulate activity of hepatic glycogen synthase and increase glycogen synthesis.

Lipid metabolism. Glucocorticoids redistribute fat. Prolonged drug intake results in accumulation of fat on the face, neck, and shoulders.

Protein metabolism. Glucocorticoids inhibit synthesis and accelerate catabolism of proteins due to utilization of amino acids in gluconeogenesis. Most significant catabolic changes are observed in lymphoid, fat, connective tissues, and skeletal muscles that leads to hypotrophy. Prolonged use of glucocorticoids is accompanied by muscular weakness, growth retardation in children, delayed wound healing, demineralisation of bone tissues, and osteoporosis. At the same, glucocorticoids stimulate erythropoiesis, production of thrombocytes, and hepatic tissue regeneration.

Influence of glucocorticoids upon water-salt balance is determinated their structure similarity to those of mineralocorticoids. Therefore, glucocorticoids promote the retention of water and salts in the body.

Besides their metabolic effects, glucocorticoids also exert a lot of pharmacological effects: anti-inflammatory, antiallergic, antitumoral, antishock effect, etc. Glucocorticoids influence cardiovascular, respiratory, gastrointestinal systems and haemopoiesis.

Anti-inflammatory effect. Glucocorticoids prevent or inhibit a development of inflammation due to inhibition of activity of macrophages and fibroblasts. Also, glucocorticoids stimulate the synthesis of lipocortins inhibiting phospholipase A_2. Phospholipase A_2 is an enzyme which frees arachidonic acid from phospholypids of cell membranes. Arachidonic acid is involved in inflammation as a substrate for the following synthesis of prostaglandins and leukotrienes. Due to inhibition of phospholipase A_2, glucocorticoids decrease the synthesis of inflammatory mediators – prostaglandins and leukotrienes.

Glucocorticoids stabilize the membranes of lysosomes and prevent the autolysis of cells. Besides, drugs stabilize the membranes of mast cells, decrease the permeability of capillaries and constrict small vessels.

These changes slow down phases I and II of inflammation (alteration and exudation). Prolonged glucocorticoid therapy is accompanied by inhibition of phase III of inflammation (proliferation): capillary ingrowth, fibroblast proliferation, collagen and mucopolysaccharide synthesis are decelerated; scar formation of connective tissue is broken.

Antiallergic effect. Glucocorticoids inhibit allergic reactions of immediate and delayed types. It is due to inhibition of T- and B-lymphocyte activity, reduction of interleukins 1 and 2 synthesis, decrease in number of circulating lymphocytes and macrophages. Glucocorticoids suppress factor inhibiting migration of macrophages, decrease an antibody titer, affect formation of complexes “antigen-antibody”, prevent interaction of these complexes with target cells, and inhibit the synthesis of mediators of allergic reactions.

Antitumoral effect of glucocorticoids results from their catabolic influence upon peptide metabolism. Glucocorticoids are used in the treatment for leucosis and other tumors.

Antishock effect of glucocorticoids is based on their ability to increase sensitivity of vascular wall to catecholamines, dopamine, and angiotensin II; elevate level of biogenic amines, and increase cardiac output.

Glucocorticoids increase gastric production of pepsin and hydrochloric acid.

In respiratory system, glucocorticoids stimulate surfactant release that increases pulmonary elasticity.

Glucocorticoids reduce number of lymphocytes and eosinophils but increase the production of erythrocytes, reticulocytes, and neutrophiles.

Glucocorticoids for systemic action are lipid-soluble compounds. In blood, glucocorticoids bind with plasma proteins; the degree of binding for synthetic agents is above 60–70 %, the binding of natural hormones is higher. In hypoproteinemia, therapeutic doses of glucocorticoids can transform to toxic doses. Drugs, which are taken orally, undergo fast and complete gastrointestinal absorption. Glucocorticoids are metabolized in the liver by ways of reduction and conjugation. Metabolits (sulfates and glucoronides) are excreted by kidneys. The metabolic rate of synthetic glucocorticoids is higher than those of natural hormones.

All glucococrticoids for systemic use penetrate placenta. Significant concentrations of dexamethasone and beclomethasone are accumulated in fetal blood that can provoke hypofunction of adrenal cortex in fetus. At the same time, hydrocortisone and prednisolone are metabolized in fetus into less toxic substances.

Inhalated glucocorticoids exert mainly local antiallergic and anti-inflammatory effects in respiratory tract. These agents are unsoluble in water.

Hydrocortisone and its esters are approved for topical application and for parenteral administration. Ointment with hydrocortisone is used to treat allergic and contact dermatitis,

eczema, neurodermatitis, etc. Hydrocortisone acetate suspension is administered into a joint cavity or intramuscularly.

Anti-inflammatory effect of prednisolone is 3–4 times higher expressed than those of hydrocortisone. Prednisolone exerts less influence upon water-salt balance. Prednisolone hemisuccinate sodium is administered intravenously. Methylprednisolone acetate is taken orally, administered parenterally, or applied topically as ointment. The drug exhibits marked anti-inflammatory and antiallergic effect.

Anti-inflammatory activity of dexamethasone is 30 times more than those of hydrocortisone. The drug exerts minimal influence upon water-salt balance. The drug is taken orally and administered parenterally (intramuscularly, intravenously, or into a joint cavity).

Triamcinolone exerts anti-inflammatory activity 5 times higher than activity of natural hormones. The drug is taken orally and administered intramuscularly or into a joint cavity. Triamcinolone does not influence water-salt balance. At the same time, triamcinolone can cause muscular atrophy, appetite loss, depression, etc.

Glucocorticoids with two fluorine atoms in molecules (synaflan and flumethasone pivalate) exert high anti-inflammatory and antiallergic activity. These agents are used topically as ointments, creams, and suspensions. Due to ability to decrease skin resistance to infections, these drugs are commonly combined with antibacterial agents (*Sinalar-H*, *Locacorten*, etc.).

Therapeutic indications for glucocorticoids are as follows:

1) severe collagenosis. As a rule, large doses of oral glucocorticoids are prescribed to treat acute attacks of rheumatism. To treat rheumatoid arthritis, glucocorticoids are taken orally or administered into a joint cavity. Treatment of systemic lupus erythematosus, scleroderma, and other collagenosis is started with intravenous administration of glucocorticoids, after that therapy is continued by oral glucocorticoids;

2) bronchial asthma. In case of severe asthma or status asthmaticus, glucocorticoids are administered intravenously during

first 1–2 days. After that, the high doses of drugs are taken orally with gradual dose decrease;

3) anaphylactic shock. High doses of glucocorticoids are administered intravenously after epinephrine injection. Besides, glucocorticoids are used in the treatment for serum sickness, contact dermatitis, etc.;

4) skin diseases (eczema, psoriasis, neurodermatitis, etc.). Topical application of drugs is preferable in these cases;

5) treatment of acute and chronic inflammatory and allergic diseases of eyes. Glucocorticoids are used in the form of eye ointment or eye drops;

6) severe intoxication in patients with infectious diseases, encephalitis, meningitis, etc. Glucocorticoids are used together with chemotherapy;

7) blood diseases: autoimmune hemolytic anemia, acute allergic purpura, thrombocytopenia, agranulocytosis, aplastic anemia, lymphosarcoma, and leucosis;

8) cranio-cerebral traumas and insults with risk of brain edema;

9) acute and chronic glomerulonephritis;

10) acute and chronic hepatitis and cirrhosis;

11) traumatic, cardiogenic, and burn shock;

12) to inhibit graft rejection in transplantation of tissues and organs;

13) acute and chronic adrenal failure (for substitutive therapy).

Glucocorticoids should be prescribed in individually tailored doses. A discontinuation of long-time therapy should be gradual with decrease of dose every 2–3 days.

Typical side effects of glucocorticoids are as follows.

1. Steroid drug withdrawal develops due to sudden discontinuation of drug intake. It is a result of atrophy or hypotrophy of adrenal cortex. Symptoms of steroid withdrawal include acute adrenal failure, aggravation of the disease treated by glucocorticoids, insomnia, nausea, vomiting, headache, myalgia, etc. Severe cases are accompanied by behavior disorders up to psychosis, generalization of inflammation with fever, pulmonary infiltrates, and other symptoms.

2. Steroid-induced diabetes mellitus.
3. Decrease of immunity and aggravation of latent infections.
4. Ulceration of stomach and intestine.
5. Osteoporosis due to calcium loss.
6. Hypertension and edemas due to sodium and water retention.
7. Psychic disorders.
8. Atrophy of skin and subcutaneous tissues.
9. Increased intraocular pressure.
10. Growth retardation in children.
11. Body weight loss.
12. Myopathy;
13. Dysmenorrhea, etc.

Presently, glucocorticoids antagonists are approved and used in medicine. *Metyrapone (Metopirone)* and *mitotane (Lysodren)* are block glucocorticoid synthesis. *Mifepristone (Mifegyne)* blocks glucocorticoid receptors. Glucocorticoid antagonists are used to treat adrenal cortex hyperthrophy (Cushing's syndrome) and to investigate corticotropin secretion. Mitotane is also used in the treatment for inoperable tumour of adrenal cortex.

Mineralocorticoids

Human adrenal cortex produces aldosterone and desoxycorticosterone. Activity of the last one is 10–20 times less than aldosterone activity. But stability of desoxycorticosterone is higher, and chemical synthesis of this hormone is possible. Thus, desoxycorticosterone preparations *desoxycorticosterone acetate* and *desoxycorticosterone trimethylacetate* are used in medicine. The drugs are administered intramuscularly, implanted subcutaneously, or taken sublingualy.

Also, synthetic mineralocorticoid *9α-fluorohydrocortisone acetate (Fludrocortisone)* is approved in medicine. The drug is 3–4 times more active than aldosterone. Moreover, fludrocortisone exerts marked anti-inflammatory effect. The drug is taken orally.

The main physiological stimulator of aldosterone secretion is angiotensin II. Aldosterone, by means of special receptors, penetrates

in nucleus of target tissue cells and stimulates the synthesis of protein – carrier of sodium. Thus, aldosterone stimulates the reabsorption of sodium and water and secretion of potassium.

Mineralocorticoid preparations are used in the treatment for chronic adrenal failure (Addison's disease). Besides, these drugs are used to treat myasthenia and adynamia because mineralocorticoids increase muscle tone and performance capability.

Overdose of mineralocorticoids is accompanied by oedemas, increased circulatory volume, and hypertension. Antagonist of mineralocorticoids is *spironolactone (Aldactone, Verospiron).* It is a potassium-sparing diuretic which is used to treat hyperaldosteronism, congestive heart failure, hepatic cirrhosis, nephrotic syndrome, etc.

Sex Hormones

Sex hormones are mainly synthesized in sex glands; some amount of sex hormones is secreted by adrenal cortex. An important function of sex hormones is formation of secondary sex characteristics: body form, distribution of fat tissue, character of voice and psyche. Besides, sex hormones regulate peptide metabolism and exert mild mineralocorticoid activity. Sex hormones are classified into female (estrogens and progestins) and male (androgens) hormones. Synthesis of sex hormones is under control of gonadotropins (follicle-stimulating and luteinizing hormones).

Preparations of Female Hormones

Estrogens and progestins are the main female hormones. Estrogens are synthezied by the theca cells of the ovarian follicle. Progestines are synthezied by the granulosa cells of the corpus luteum.

Estrogens

Classification of estrogen preparations:

1) native estrogens: *estron, estriol,* and *estradiol;*

2) semisynthetic estrogens: *ethinylestradiol (Microfollin)* and *methylestradiol;*

3) synthetic estrogens: *hexestrol (Sinestrol), sigetin,* and *diethylstilbestrol.*

A main site of estrogens synthesis is ovarian follicles. Besides, these hormones are also synthesized by adrenal cortex and placenta. In male body, small amount of estrogens is synthesized by testicles. Estrogens provide development of secondary sex characteristics in females, prepare uterus to ovule implantation, control endometrium proliferation, and myometrium hypertrophy, influence growth and functional activity of lacteal glands.

A main target organ of estrogens is uterus, where they stimulate synthesis of contractile proteins. Estrogens improve energy metabolism and promote accumulation of glycogen, glucose, and ATP in myometrium. Estrogens increase myometrium excitability and its ability to spontaneous generation of action potentials. It is accompanied by increase of amplitude and frequency of uterine contractions. Estrogens increase myometrium sensitivity to oxytocin.

It should be noticed that long-lasting increase of estrogens concentration with simultaneous reduction of progestins level may lead to pathologically excesive protein synthesis and carcinogenesis.

Effects of estrogens is not limited by their influence on myometrium. Hormones promote accumulation of nitrogen, calcium, and phosphorus in a body. Estrogens improve glucose utilization due to increase of tissue sensitivity to insulin. Also, estrogens increase concentration of iron and copper in a body and activate renin-angiotensin system. Estrogens stimulate synthesis of antibodies, formation of macrophages, function of phagocytes, increase resistance to infections.

Therapeutic indications of estrogens are as follows.

1. Stimulation of uterine contraction in labor.

2. Osteoporosis in postmenopausal women.

3. Substitutive therapy in ovarian hypofunction. Estrogens are used to treat infantilism (retardation of sexual development), dysmenorrhea, amenorrhea, sterility, and menopause.

4. Breast cancer after menopause (after 60 years of age).

5. Disfunctional uterine bleeding.

6. Prostate cancer. Estrogens are effective due to their ability to bind to androgen receptors.

7. Peroral contraception (together with progestins).

For substitutive therapy, estrogens are used in menopausal period and after ovariectomy. *Progynova* (estradiol valerate), *Climara* (transdermal estradiol), *Climodien* (estradiol valerate and dienogest), and *Klimonorm* (estradiol valerate with levonorgestrel), etc. are most commonly used with this end in view.

Side effects of estrogens are oedemas, headache, hypertension, thrombophlebitis, uterine bleeding, renal and hepatic dysfunction. In males, estrogens cause feminization (development of female secondary sex characteristics) and decrease of potency.

Due to their ability to stimulate tissue proliferation, estrogens are prescribed with caution in women with tumoral diseases, mastopathy, and after 40 years old.

Antiestrogens

Antiestrogens are analogues of synthetic estrogens: *clomiphene (Clostilbegyt)* and *tamoxifen (Nolvadex)*.

Clomiphene, taken in low doses, easily penetrates blood-brain barrier and blocks interaction of estrogens with specific receptors in hypothalamus and hypophysis. Due to negative feedback, it increases secretion of pituitary gonadotropins which promote ovulation. Clomiphene is used in the treatment for infertility in women and oligospermia.

Tamoxifen does not penetrate central nervous system. Therefore, the drug blocks peripheral estrogen's receptors in mammary glands and endometrium. Tamoxifen is used in the treatment for estrogen-dependent tumors of mammary glands and endometrium.

Progestins

Progestins are effective synthetic versions of progesterone. Progesterone is synthesized by the corpus luteum and adrenal cortex. During pregnancy, progesterone is synthesized by placenta. Progesterone prepares endometrium to implantation, promotes intensive proliferation of endometrial glands and placenta formation, and prevents ovulation due to inhibition of the production of pituitary hormones. Progesterone promotes synthesis of proteins in the uterus. Progesterone inhibits uterine excitability, increases membrane resting potential of smooth muscles of the uterus (hyperpolarization) that decreases spontaneous activity of myometrium. In other organs, progesterone exerts catabolic influence upon protein metabolism and causes negative nitrogen balance.

Progestin preparations are classified as follows.

1. Native hormone: *progesterone*.
2. Synthetic preparations: *oxyprogesterone capronate, pregnin, allylestrenol (Turinal), medroxyprogesterone acetate (Depo-Provera), norethisterone (Norcolut)*, etc.

Progestin preparations are characterized by different activity and duration of action. Progesterone exerts fast and short-time effect. The drug is administered intramuscularly everyday. Oxyprogesterone capronate acts during 7–14 days. Activity of pregnin is 5–15 times less than those of progesterone. Pregnin is taken sublingually. Allylestrenol is a synthetic progestin with highest activity. Norethisterone exerts progestin and androgen activity in ratio 1 : 1. Its duration of action is about 24 hours. Norethysterone is used to treat endometriosis, dismenorrhea, uterine myoma, glandular hyperplasia, and endometrial polyps. Depo-Provera is administered intramuscularly or taken orally. Its duration of action is about 3 months.

Therapeutic indications for progestins are as follows.

1. Habitual abortion in early pregnancy.
2. Dismenorrhea.
3. Premenstrual syndrome.
4. Contraception (in combination with estrogens or alone).

5. Disfunctional uterus bleeding due to corpus luteal insufficiency.

6. Estrogen-dependent cancer of mammary glands, endometriosis, androgen-dependent adenoma and prostate cancer.

7. Infertility.

Side effects of progestins are hypertension, oedemas, headache, nausea, depression, feeling tired, dysfunctional uterine bleeding, etc.

Anti-progestins

Mifepristone (RU 486) is an agent with anti-progestin activity. The drug interacts with progestin receptors that prevents progesterone binding with those. Mifepristone stimulates uterine contraction and causes abortion. The drug is used in medicine to interrupt pregnancy. The drug significantly increases uterine sensitivity to prostaglandins; therefore, mifepristone is commonly combined with them. Besides, mifepristone is used to normalize menstrual cycle.

Hormonal Contraceptives

Contraceptives are used to birth control and to prevent unwanted pregnancies.

Hormonal contraceptives are classified as follows.

1. Co-formulated estrogen-progestin-containing drugs.
2. Drugs containing microdoses of progestins.
3. Prolonged progestin-containing drugs (depot-contraceptives).
4. Postcoital contraceptives.
5. Vaginal contraceptives.
6. Male's contraceptives.

Combined Estrogen-Progestin Containing Drugs

Co-formulation of estrogen with progesterone for oral contraception was proposed by Pincus in 1955. In Europe, 35–51 % women use this method of contraception. *Ethinylestradiol* is most commonly used estrogen for such co-formulations. Testosterone derivatives (*norethisterone, norgestrel, and levonorgestrel)* are progestins which most commonly included in these drugs.

Combined estrogen-progestin containing contraceptives prevent ovulation due to inhibition of gonadotropins secretion according to principle of negative feedback. Besides, these drugs prevent ovum fertilization by means of progestin which inhibits motility of Fallopian tubes and increases time of ovum moving in uterine cavity. Simultaneously, viscocity and acidity of cervical mucus is increased that prevents spermatosoids moving in uterine cavity and promotes their destruction. Combined contraceptives worsen conditions for implantation of fertilized ovum because progestin accelerates onset secretory phase in endometrium, violates its metabolism and stimulates degeneration. In such conditions, ovum implantation and development of pregnancy become impossible.

There are monophasic, biphasic, and triphasic estrogen-progestin-containing drugs.

Monophasic and biphasic preparations are taken from 5th days of menstrual cycle, while triphasic drugs are taken from 1st day. Drugs are taken for 21 days, after that 7-days break is necessary when withdrawal bleeding occurs. Prolongation of break to 8–9 days is impossible because it increases risk of pregnancy due to spontaneous ovulation.

Monophasic preparations include such drugs as *Ovidon, Rigevidon, Diane-35, Non-Ovlon, Marvelon, Femoden,* etc. These drugs contain constant concentrations of estrogen and progestin.

In biphasic contraceptives, concentration of progestin in second phase of cycle is increased. These drugs include *Neo-Eunomin, Anteovin,* etc.

In triphasic drugs, progestin concentration is increased gradually in three steps, whereas estrogen concentration in first and third phases is constant. Representatives of triphasic contraceptives are *Triquilar, Trisiston, Tri-Regol, Trinovum,* etc.

Presently, monophasic drugs became preferable due to appearance of III-generation progestins (desogestrel, gestodene, norgestimate) exerting high affinity to progestin receptors and safety.

Estrogen-progestin containing contraceptives are readily absorbed from gastrointestinal tract. Their bioavailability is about 70 %. These drugs are metabolized in liver by way of conjugation with glucuronic or sulfuric acid and excreted by kidneys.

Estrogen-progestin containing drugs are taken orally in the same time of day. Long-lasting regular drug intake (more than 2 years) is accompanied by normalization of menstrual cycle, elimination of dysmenorrhea and premenstrual syndrome, reduced risk of inflammatory diseases of pelvic organs, decreased risk of cancer of endometrium and ovaries, fibromyoma, iron deficiency anemias, etc.

Besides contraception, co-formulated estrogen-progestin drugs are used to treat endometriosis, dysmenorrhea, amenorrhea, and some form of infertility.

It should be noticed that a probability of pregnancy is increased after discontinuation of drugs intake.

Side effects of co-formulated drugs are observed most commonly during initial 1–2 monthes of therapy. After this time, their frequence is reduced to 5–10 %. Most common side effects are increased blood coagulation with risk of venous thrombosis and thromboembolism, hepatic dysfunction, headache, dizzinnes, nausea, body wheight gain, intermenstrual bleeding, etc.

Estrogen-progestin containing drugs are contraindicated in pregnancy, hypertensive disease, ischemic heart disease, obesity, predisposition to thromboembolism, hepatic and oncological diseases, and for smoking women after 35 years old.

Contraceptives Containing Microdoses of Progestins

Contraceptives containing microdoses of progestins include such drugs as *Exluton (lynestrenol), Microlut (levonorgestrel), Continuin (ethynodiol diacetate), Ovral (norgestrel),* etc.

Progestin containing contraceptives are prescribed in cases when estrogen-progestin co-formulated drugs are contraindicated. Responsibility of these drugs is less.

Mechanism of action of these drugs is not clear enough. It is supposed that progestins change amount and contents of cervical

mucus that interfere spermatosoids to penetrate through it. Besides, progestin-containing drugs slow down ovum moving in fallopian tubes and change characteristics of endometrium, therefore, these drugs that interfere ovum implantation. Inhibition of hypothalamic-pituitary regulation is also possible.

Maximal effect of these drugs develops in 3–4 hours after intake and lasts 16–19 hours. Disadvantages of progestin-containing contraceptives are their less efficacy in comparison with estrogen-progestin co-formulations, necessity of more close dosage regimen, irregular menstrual cycle, intermenstrual bleeding, etc.

Prolonged Progestin-Containing Contraceptives

There are the following prolonged progestin-containing contraceptives.

1. Drugs for injections: *medroxyprogesterone acetate (Depo-Provera)*. The drug is administered intramuscularly 1 time in 3–4 months.

2. Subcutaneous implants: *Norplant (levonorgestrel-releasing implant)*. Five capsules of Norplant are implanted under the skin of forearm. Its duration of action is about 5 years.

3. Intrauterine drugs: *Mirena*. It is intrauterine contraceptive device permanently releasing levonorgestrel for 5 years. Mirena exerts high contraceptive responsibility. The drug decreases frequency and volume of uterine bleeding and is aspecially intended for women suffering from menorrhagia and dysmenorrhea.

Side effects of prolonged progestin-containing drugs are body weight gain, decreased libido, intermenstrual bleeding, hair loss, etc.

Postcoital Contraceptives

Postcoital contraceptives are represented by *Postinor* and *Escapel*. Both drugs contain levonorgestrel. Poscoital contraceptives violate secretory phase of menstrual cycle and cause temporal atrophic changes in ovaries. These drugs are intended for contraception in women who do not use contraceptives regullary. Postcoital contraceptives are taken immidiatly after coitus but not oftener than 1 time per week (4 times per a month).

Vaginal Contraceptives

Vaginal contraceptives are represented by *benzalkonium chloride (Pharmatex)* and *nonoxynol (Patentex oval, Conceptrol)*. These drugs violet cellular membrane of spermatosoids that leads to their disruption.

Male Contraceptives

Male contraceptives are represented by *gossypol* and *inhibin*. Their mechanism of action is associated with inhibition of spermatogenesis and semen maturation.

Gossypol is obtained from cottonseed oil. At daily drug intake, its effect develops in 2 months. Spermatogenesis is restored in 3 months after discontinuation of gossypol intake. Often side effect of gossypol is hypokalemia. The drug provokes infertility in about 20 % of males who taken it.

Inhibin affects hypothalamic-pituitary regulation of male sex glands. The drug selectively inhibits a follicle-stimulating hormone release that leads to violation of spermatogenesis without influence upon testosterone production. Inhibin is obtained from seminal fluid of males.

Preparations of Male Hormones (Androgens)

About 6 mg of androgens are synthesized in males mainly in interstitial Leydig's cells and, partly, in cells of adrenal cortex. In females, certain quantity of androgens (nearly 0.3 mg/day) is synthesized by adrenal cortex and ovarian follicular cells.

Biological effects of androgens are determined by testosterone and its metabolites – androstenediol, dihydrotestosterone, etc. Androgens influence formation of primary and secondary sex characteristics of males, promote normal development of prostate and reproductive organs. Androgens regulate spermatogenesis and potency. Besides, androgens stimulate protein synthesis (anabolic effect) and suppress protein catabolism. In females, small doses of

androgens stimulate synthesis of gonadotropins, while large doses block this process.

Androgens increase renal reabsorption of sodium, calcium, chlorine, and equivalent volume of water. Also, hormones promote the deposition of calcium in bones, increase activity of some enzymes and somatotropin. It is accompanied by activation of tissue respiration, oxidative phosphorylation, and energy accumulation. Androgens stimulate synthesis of erythropoietins and increase the heart contractile function.

The following synthetic analogues of androgens are used as medical preparations: *testosterone propionate, methyltestosterone, testosterone enanthate (Testenate Depot), Sustanon-250,* etc.

Testosterone and testosterone enanthate are manufactured as ampoules filled with oil solutions. Testosterone propionate is dosed intramuscularly 1 time in 2 days, testosterone enanthate – once in 3–4 weeks. Methyltestosterone is taken sublingually 1–5 times a day. Sustanon-250 is a co-formulated androgen preparation containing several testosterone ethers with different duration of action. The effect of Sustanon-250 starts just after administration and lasts about 3–4 weeks. Therefore, this drug is administered intramuscularly once in 3–4 weeks. Sustanon-250 is a drug of choice for prolonged hormone-replacement therapy.

There are testosterone preparations for subcutaneous implantation in a fat of the abdominal wall. Implants are administered in dose 0.4–0.6 g every 4–6 months. Testosterone implants is the most appropriate form for maintenance of stable testosterone dose for 6 months. But in practice, the implants are not in wide use due to infections and implant extrusion.

Recently, androgens are available for transdermal administration in forms of skin gel or special patch.

There are the following therapeutic indicaiotns for androgens:

– replacement therapy of sexual failure in males (e. g., infantilism, erectile dysfunction);

– osteoporosis;

– cancer of mammary glands, uterus, and ovaries in women younger than 60 years of age.

Side effects of androgens are increased sex arousal, masculinization in women, cholestatic jaundice, oedemas, nausea, hypercalcemia, etc.

Antiandrogens

Synthesis of testosterone can be suppressed by means of hypothalamic hormone *gonadorelin* and its synthetic analogue *leuprolide*. The drugs are used to treat prostatic hyperplasia. But the following groups of antiandrogens are used more widely:

– androgen receptor blocking drugs: *cyproterone acetate, flutamide*.

– 5α-reductase inhibitors (enzyme catalyzing transformation of testosterone to dihydrotestosterone): *finasteride (Proscar), dutasteride*.

Androgen receptor blocking drugs inhibit spermatogenesis due to blockage of androgen receptors. Their effect persists during 4 months after removal of drug intake. besides, these drugs block androgen receptors in the central nervous system that leads to decrease of libido and impotence. Cyproterone and flutamide are used to treat prostate cancer, compulsive sexual behaviour, androgenization in women, etc.

5α-reductase inhibitors suppress activity of enzyme catalyzing transformation of testosterone to dihydrotestosterone. Finasteride is used in the treatment for prostatic adenoma. The agent reduces the sizes of prostate and improves the urination in 1/3 of patients. As a rule, finasteride does not influence libido and potency.

Anabolic Steroids

A group of anabolic steroids includes such drugs as *methandrostenolone, nandrolone decanoate (Retabolil), nandrolone phenylpropionate (Fenobolin), oxandrolone, stanozolol, silabolin*, etc.

Anabolic steroids activate iRNA synthesis that results in the increase of protein synthesis. Therapy by anabolic steroids is accompanied by accumulation of nitrogen, potassium, sulfur, phosphorus, and calcium in the body. Anabolic steroids stimulate

regenerative processes, increases muscular mass, improves appetite and general state of patients.

Methandrostenolone is a drug with short duration of action. Its tablets are taken orally 1–2 times a day. Fenobolin and Retabolil are dosed intramuscularly. Duration of action of Fenobolin is 7–15 days. The effect of Retabolil lasts about 3 weeks.

Therapeutic indications for anabolic steroids are as follows:

– chronic infections (e. g., tuberculosis);
– recovery period after serious exhausting diseases;
– thyrotoxicosis;
– dystrophy in children;
– diseases of musculoskeletal system;
– paralysis;
– osteoporosis;
– bone fractures;
– chronic heart failure;
– postinfarction period;
– cirrhosis;
– chronic renal diseases, etc.

Side effects of anabolic steroids are oedemas, excessive accumulation of calcium in bones, hepatic dysfunction, and masculinization in females. Anabolic steroids are contraindicated in pregnancy, period of lactation, prostatic carcinoma, and some hepatic diseases.

Table 12 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Hydrocortisoni acetas	Intrasinovially 0.005–0.025 g 1 time in 3 days; intramuscularly 0.025 g 2–6 times a day; in eye 0.5 % ointment	Vials 5 ml of 2.5 % suspension; eye ointment 0.5 % – 2.5 g
Prednisolonum	Orally 0.005–0.05 g 2 times a day; on injured part of skin 0.5 % ointment	Tablets 0.005 g; ointment 0.5 % – 10.0 g or 20.0 g

Continuation of the table 12

Drug name (Latin)	Single dose and route of administration	Drug product
Prednisolini hemisuccinas	Intravenously or intramuscularly 0.05–0.2 g 2–6 times a day	Ampoules 0.025 g of powder for injection
Dexamethasonum	Orally 0.000 5–0.001 g 2–3 times a day	Tablets 0.000 5 g
Synaflanum	On injured part of skin 0.025 % ointment	Ointment 0.025 % – 10.0 or 15.0 g
Beclomethasoni dipropionas	2 inhalations 3–4 times a day	Aerosol “Becotide” or “Beclomet”
Desoxycorticosteroni acetas	Sublingually 0.005 g daily; intramuscularly 0.005 g 1 time in 2 days – 0.01 g 1–4 times a day	Tablets 0.005 g; ampoules 1ml of 0.5 % oil solution
Oestronum	Intramuscularly 5 000–10 000 IU 1 time a day	Ampoules 1 ml of 0.05% or 0.1% solution (5 000 IU and 10 000 IU respectively)
Synoestrolum	Orally or intramuscularly 0.001 g 1–2 times a day	Tablets 0.001 g; ampoules 1 ml of 0.1% or 2% oil solution
Progesteronum	Intramuscularly 0.005–0.015 g 1 time a day or 1 time per 2 days	Ampoules 1 ml of 1% or 2.5% oil solution
Turinalum	Orally 0.005 g 2–3 times a day	Tablets 0.005 g
Testosteroni propionas	Intramuscularly 0.01–0.025 g 1 time per 2 days	Ampoules 1 ml of 1% or 5% oil solution
Phenobolinum	Intramuscularly 0.025–0.05 g 1 time per 7–10 days	Ampoules 1 ml of 1% or 2.5% oil solution
Retabolilum	Intramuscularly 0.025–0.05 g 1 time per 2–3 weeks	Ampoules 1 ml of 5% oil solution

Step 1. Tasks for Self-Control
Hormonal Drugs

1. A patient with diabetes mellitus experienced loss of consciousness and convulsions after an injection on insulin. What might be the result of biochemical blood analysis for concentration of sugar?

A. 5.5 mmol/*l*.

B. 10.0 mmol/*l*.

C. 8.0 mmol/*l*.

D. 1.5 mmol/*l*.

E. 3.3 mmol/*l*.

2. A patient with diabetes didn't get insulin injection in time that caused hyperglycaemic coma (glucose in blood is 50 mmol/*l*). What mechanism is prevalent in the development of coma?

A. Hyperosmia.

B. Acidosis.

C. Hypoxia.

D. Hyponatremia.

E. Hypokalaemia.

3. A 56-year-old patient complaining of thirst and frequent urination was diagnosed with diabetes mellitus. Butamidum was prescribed. How does this drug act?

A. It relieves transport of glucose through the cell membranes.

B. It helps to absorb glucose by the cells of the organism tissues.

C. It inhibits α-cells of Langerhans islets.

D. It inhibits absorption of glucose in the intestines.

E. It stimulates β-cells of Langerhans islets.

4. Testosterone and its analogues increase the mass of skeletal muscles that allows to use them for treatment of dystrophy. Due to interaction of the hormone with what cell substance is this action caused?

A. Chromatin.

B. Proteins-activators transcription.

C. Nuclear receptors.

D. Membrane receptors.

E. Ribosomes.

5. A patient had been taking glucocorticoids for a long time. When the drug was withdrawn, he developed the symptoms of disease aggravation, decreased blood pressure, and weakness. What is the reason of this condition?

A. Cumulation.

B. Hyperproduction of ACTH.

C. Sensibilisation.

D. Habituation.

E. Appearance of adrenal insufficiency.

6. A patient with infectious mononucleosis had been taking glucocorticoids for two weeks. He was brought into remission, but he fell ill with acute attack of chronic tonsillitis. What action of glucocorticoids caused this complication?

A. Antitoxic.

B. Anti-inflammatory.

C. Immunosuppressive.

D. Antiallergic.

E. Antishock.

7. A patient was on glucocorticoids for a long time, discontinuation of usage caused exacerbation of the illness, decreased BP, and weakness. How can you explain it?

A. Cumulation.

B. Insufficiency of adrenal glands.

C. Adaptation to the drug.

D. Sensitization.

E. Hyperproduction of ACTH.

8. Usage of oral contraceptives with sex hormones inhibits secretion of the hypophyseal hormones. Secretion of which of the indicated hormones is inhibited while using oral contraceptives with sex hormones?

A. Vasopressin.

B. Thyrotropic.

C. Somatotropic.

D. Follicle-stimulating.

E. Oxytocin.

9. Because of a long-term drug application such complications as osteoporosis, erosive ulcers of the mucous coat of stomach, oedemas, increase of arterial pressure, and insomnia have developed. Laboratory tests detected hypernatremia, hypokalaemia, and hyperglycaemia. What drug has been applied?

A. Reserpine.

B. Hypothiazidum.

C. Prednisolone.

D. Indomethacin.

E. Digoxin.

10. Having a serious infection a patient needs an anabolic drug for the improvement of appetite. Which one?

A. Retabolil.

B. Thiamine chloride.

C. Tinctura of wormwood (Tinctura Absinthii).

D. Heparin.

E. Folic acid.

11. A medicine was prescribed for treatment of arthritis. It has the following pharmacological characteristics: it increases the production of lipomoduline, reduces phospholipase A_2 activity, reduces the synthesis of arachidonic acid metabolism products (cyclic endoperoxides, prostaglandins). What drug is this?

A. Glibenclamide.

B. Adrenaline hydrochloride.

C. Isadrinum

D. Prednisolone.

E. Butadione.

12. A patient in soporous condition is delivered to endocrinologic unit. The increasing sweating and smell of acetone from the mouth are observed. The level of glucose in blood is 22.43 mmol/*l*. The diagnosis is hyperglycemic coma. What hypoglycemic drug should be administered to the patient?

A. Drug from sulfonylurea derivatives group.

B. Insulin with intermediate duration of action.

C. Insulin with long duration of action.

D. Drug from biguanides group.

E. Insulin with short duration of action.

13. The treatment of the first type of diabetes mellitus foresees the imitation of basic and carbohydrate-induced secretion of insulin. What drug does imitate the carbohydrate-induced secretion of insulin?

A. Suinsulin.

B. Zinc-insulin.

C. Glibenclamide.

D. Metformin.

E. Glibutidum.

14. A patient with asthmatic status is delivered to urgent unit. The patient is suffering from bronchial asthma for 12 years. Earlier attacks were reduced by salbutamol but now this drug is ineffective. What drug should be administered to the patient first of all?

A. Bisacodyl.

B. Acyclovir.

C. Oxytocin.

D. Prednisolone.

E. Famotidine.

15. Deficiency of birth activity has developed in a woman during delivery. What drug should be administered to woman for restoration of contractive activity of myometrium?

A. Dithylinum.

B. Dimedrol.

C. Unithiol.

D. Aminazine.

E. Oxytocin.

16. A woman with acute glomerulonephritis is delivered to nephrology unit. What drug should be prescribed to her?

A. Bisacodyl.

B. Prazosin.

C. Prednisolone.

D. Phenazepam.

E. Spirituous solution of iodine.

17. To prevent the transplant rejection after organ transplantation it is required to administer hormonotherapy for the purpose of immunosupression. What hormones are used for this purpose?

A. Catecholamines.

B. Mineralocorticoids.

C. Glucocorticoids.

D. Thyroid hormones.

E. Sexual hormones.

18. Continuous use of a certain drug may cause osteoporosis, erosions of stomach mucosa, hypokalaemia, retention of sodium and water in the organism, decreased concentration of corticotropin in the blood. What drug is it?

A. Prednisolone.

B. Hypothiazid.

C. Reserpine.

D. Digoxin.

E. Indomethacin.

19. An elderly female patient suffers from the type 2 diabetes mellitus accompanied by obesity, atherosclerosis, and coronary artery disease. Basal hyperinsulinemia is also present. What treatment would be the most appropriate?

A. Amlodipine.

B. Retabolil.

C. Glibenclamide.

D. Insulin.

E. Lovastatin.

20. A woman with bronchial asthma has been using prednisolone in tablets for two months. Owing to significant improving of condition, she suddenly stops drug intake. Which complication is possible in this case?

A. Stomach bleeding.

B. Cushing's syndrome.

C. Obesity.

D. Hypotension.

E. Withdrawal syndrome.

21. A patient with rheumatoid arthritis has been using prednisolone for a long time. Why should he avoid the contacts with infectious patients?

A. Owing to development of secondary immunodeficiency.

B. Owing to blockage of interferon synthesis.

C. Owing to ability of thrombosis.

D. Owing to development of lymphopenia.

E. Owing to possibility of arthritis aggravation.

22. In experiment, hydrocortisone (intramuscularly, in dose 1 g/kg) was administered to rats. The development of stomach ulcers was observed after 10 injections. What is the mechanism of ulceration?

A. Hyperacidity.

B. Decrease of gastrin secretion.

C. Hypersecretion of mucus.

D. Embolism of vessels.

E. Ischemia of the stomach mucosa.

23. Sugar in the urine was not found in examination of patient with diabetes mellitus. What is the tactic of physician for this patient?

A. Without any remedial measures.

B. Prescribe insulin.

C. Prescribe insulin and glibenclamide.

D. Prescribe glibenclamide.

E. Don’t prescribe antidiabetic therapy and use carbohydrate diet.

24. A patient suffers from insulin-dependent diabetes mellitus. Endocrinologist prescribes to him insulin and recommends to avoid stress because increase of adrenaline level in stress is accompanied by elevation of glucose level from glycogen in skeletal muscles. Which link of the regulation of glycogenolysis by adrenaline is affected by insulin?

A. Activation of protein kinase.

B. Synthesis of cAMP.

C. Stimulation of phosphodiesterase.

D. Inhibition of protein phosphatase.

E. Activation of adenylyl cyclase.

25. A patient is unconscious with the smell of acetone from the mouth. A doctor has diagnosed diabetic coma. Which drug should be administered to the patient for interruption of coma?

A. Acarbose.

B. Chlorpropamide.

C. Buformin.

D. Insulin.

E. Glipizide.

26. A patient on the third day after thyroidectomy has seizures. Which drug should be prescribed to him?

A. Phenobarbital.

B. Potassium chloride.

C. Calcium chloride.

D. Potassium bromide.

E. Neuroleptics.

27. Excessive granulations have developed in a patient with chronic inflammatory processes of the skin. Specify the hormonal drug which should be used in treatment of this patient.

A. Mineralocorticoids.

B. Glucocorticoids.

C. Thyroxine.

D. Somatotropin.

E. Insulin.

28. Hormonal therapy is compulsory for suppression of autoimmune reactions after organ transplantation. Which hormones are used for this aim?

A. Sex hormones.

B. Mineralocorticoids.

C. Adrenaline.

D. Glucocorticoids.

E. Somatotropin.

29. Glucocorticoids are widely used in modern clinical practice. Specify the effect which is achieved only with administration of high doses of glucocorticoids.

A. Increase of sodium excretion.

B. Suppression of inflammation.

C. Support of normal vessels tone.

D. Increase of water excretion.

E. Inhibition of adrenocorticotropin secretion.

30. A significant increase of diuresis is developed in a 50-year-old woman after infective disease of brain. The glucose blood level is 4.1 mmol/*l*. A doctor diagnosed the lack of endocrine function. What hormone deficiency is most likely?

A. Cortisone.

B. Vasopressin.

C. Aldosterone.

D. Glucagon.

E. Insulin.

31. Massive glucocorticoids therapy in patient with rheumatism results in hyperuricemia. Indicate metabolic process owing to change in which hyperuricemia is released.

A. Intensive lipolysis.

B. Activation of gluconeogenesis.

C. Intensive catabolism of proteins.

D. Intensive catabolism of pyrimidine nucleotides.

E. Intensive degradation of purine nucleotides.

32. A patient is admitted to the hospital with the diagnosis of lobar pneumonia. Doctor prescribes to him injections of benzylpenicillin. An injection of antibiotic results in development of anaphylactic shock in patient. Choose the hormonal drug which should be administered for rescue emergency care.

A. Dimedrole.

B. Adrenaline.

C. Prednisolone hemisuccinate.

D. Calcium chloride.

E. Euphyllinum.

33. A doctor recommended iodine-containing drugs to liquidators, the victims of the Chernobyl nuclear power plant. What is the aim of this recommendation?

A. Increase of iodine storage in organism.

B. Compensation of iodine deficiency in organism.

C. Compensation of iodine deficiency in thyroid gland.

D. Preventive saturation of thyroid gland with nonradioactive iodine.

E. Replacement of radioactive iodine by nonradioactive iodine.

34. Long-term use of drug A. can cause osteoporosis, erosions of the gastric mucosa, hypokalemia, sodium and water retention in the body, reducing the content of corticotropin in the blood. Identify the product.

A. Indomethacin.

B. Reserpine.

C. Hydrochlorthiazide.

D. Prednisolone.

E. Digoxin.

35. A woman has been a habitual miscarriage. Identify the drug which should be prescribed to the woman for pregnancy saving.

A. Hydrocortisone.

B. Methandrostenolone.

C. Progesterone.

D. Estron.

E. Testosterone.

36. Explain why corticotropin is administered in the morning?

A. Drug doesn't influence upon sleep structure.

B. For compensation of glucose level decrease after sleep.

C. For maintenance of necessary daily hormone concentration.

D. Drug doesn't cause ulceration of stomach in the morning.

E. According to natural rhythm of hormone synthesis.

37. A 63-year-old woman suffers from diabetes mellitus. Endocrinologist prescribes to her butamide. What is the mechanism of butamide action?

A. Drug stimulates the hypothalamus.

B. Increase of glucose degradation.

C. Drug directly provides the transport of glucose into the cells.

D. Drug increases the degradation of proteins.

E. Activation of pancreatic islet beta-cells.

38. A doctor prescribed to a 60-year-old woman after mastectomy synthetic drug which reduced simulative influence of estrogens upon tumor growth. Identify this drug.

A. Cisplatin.

B. Tamoxifen.

C. Rubomycin.

D. Diethystilbestrol.

E. Fosfestrol.

39. A doctor prescribed butadionum to patient with diabetes mellitus who was treated with butamide. After butadionum intake, hypoglycaemia developed in this patient. What is the cause of this complication?

A. Butadionum replaces butamide from the binding with plasma proteins.

B. Increase of butamide biotransformation.

C. Increase of butamide excretion.

D. Competition of drugs for connection with receptors.

E. Pharmaceutical incompatibility of drugs.

40. A 60-year-old patient with diabetes mellitus receives insulin semilente for correction of hyperglycemia. 10 days ago, he began treatment of hypertensive disease. In an hour after reception of hypotensive drug patient felt weakness, dizziness, decrease of blood pressure, and in few minutes later the patient lost consciousness. Identify pathological state which developed.

A. All answers are incorrect.

B. Acute disturbance of cerebral circulation.

C. Cardiogenic shock.

D. Hypoglycemic coma.

E. Hyperglycemic coma.

41. Hyperglycemic coma develops in a patient with diabetes mellitus. Glucose concentration in the blood is 18.44 mmol/*l*. Which drug should be administered to the patient?

A. Sulfonylurea derivative.

B. Biguanide derivative.

C. Insulin with short action.

D. Insulin with long action.

E. Insulin with intermediate duration of action.

42. Mercazolil (thiamazole, methimazole) is prescribed to a patient with thyrotoxicosis. What is the mechanism of drug action?

A. Mercazolil blocks the release of hormones by thyroid gland.

B. Mercazolil suppresses the activity of thyrotropin.

C. Mercazolil blocks the incorporation of iodine in hormones molecules.

D. Mercazolil destroys the tissue of thyroid gland.

E. Mercazolil decreases the synthesis of thyroxine in thyroid gland.

43. Iodine-containing drug is prescribed to a patient with initial stage of hyperthyroidism. Which effect is the basis of antithyroid action of this drug?

A. Destruction of tissue of thyroid gland.

B. Inhibition of thyrotropin secretion by pituitary.

C. Inhibition of enzymes synthesizing thyroid hormones.

D. Blockage of iodine incorporation in the structure of hormones.

E. Inhibition of thyrotropin-releasing hormone secretion by hypothalamus.

44. Hypoglycemic drug A was prescribed to a patient with diabetes mellitus. In several weeks of treatment, the glucose level in blood is decreased. But lactic acidosis develops in patient. Identify the group of hypoglycemic drugs for which this complication is most typical.

A. Sulfonylurea derivatives.

B. Insulins with short action.

C. Biguanides.

D. Insulins of long duration of action.

E. Combined insulins.

45. A patient with infectious mononucleosis took glucocorticoids for 2 weeks. Owing this treatment, the remission of infectious mononucleosis is developed in the patient. But aggravation of chronic tonsillitis also arises in him. What is the cause of this complication?

A. Antioxidant effect of glucocorticoids.

B. Anti-shock effect of glucocorticoids.

C. Anti-inflammatory effect of glucocorticoids.

D. Antiallergic effect of glucocorticoids.

E. Immunosuppressive effect of glucocorticoids.

46. The increased glucose blood concentration is revealed in a patient with neurodermatitis which is using dexamethasone for a long time. Identify the metabolic effect of glucocorticoids which results in this complication.

A. Activation of gluconeogenesis.

B. Increase of glucose absorption in intestine.

C. Inhibition of glycogen synthesis.

D. Increase of insulin degradation.

E. Activation of glycogen synthesis.

47. A patient uses prednisolone in tablets for treatment with bronchial asthma. Doctor recommends to replace prednisolone by dexamethasone. How many times should be less the dose of dexamethasone in comparison with prednisolone?

A. 4 times.

B. 20 times.

C. 2 times.

D. 7 times.

E. 50 times.

48. In a 43-year-old patient the glucose is determined in urine for the first time. Which drug should be prescribed to him?

A. Saccharose.

B. Butamide.

C. Oxytocin.

D. Allopurinol.

E. Vasopressin.

49. A 38-year-old woman went to the Cancer Centre with tumor of the breast. After mastectomy doctor prescribes to woman antitumoral hormonal drug. Identify this drug.

A. Testosterone.

B. Myelosanum.

C. Sarcolysin.

D. Progesterone.

E. Fosfestrol.

50. A doctor administers prednisolone for increase of blood pressure in patient with acute vessels insufficiency. Why glucocorticoids increase blood presse?

A. Glucocorticoids cause redistribution of blood in organism.

B. Glucocorticoids cause retention of water in organism.

C. Glucocorticoids directly stimulate alpha-adrenergic receptors of vessels.

D. Glucocorticoids decrease the sensitivity of cholinoreceptors to acetylcholine.

E. Glucocorticoids increase sensitivity of adrenergic receptors to catecholamines.

51. A doctor prescribes finasteride (Proscar) to patient with benign hyperplasia of the prostate. What is the mechanism of antiandrogenic action of this drug?

A. Blockage of androgenic receptors.

B. Inhibition of androgens synthesis.

C. Inhibition of androgens secretion.

D. Inhibition of enzyme 5-alpha-reductase which promotes the transformation of testosterone into the dihydrotestosterone.

E. Inhibition of gonadotropin synthesis.

52. A 65-year-old woman has applied to orthopedic department with complaints of pain in the left leg. Medical examination has found the symptoms of osteoporosis and aseptic necrosis of femoral head. Which drug should be prescribed for treatment of this woman?

A. Cyanocobalamin.

B. Calcitonin.

C. Ergocalciferol.

D. Calcium gluconate.

E. Methionine.

53. A 60-year-old patient is suffering from diabetes mellitus and receiving insulin semilente for correction of hyperglycemia. 10 days ago, he began treatment of hypertensive disease with certain drug. In an hour after drug intake, hypoglycemic coma is developed in the patient. Which of the following drug can cause this complication?

A. Nifedipine.

B. Anaprilinum.

C. Verapamil.

D. Captopril.

E. Prazosin.

54. A 60-year-old patient is suffering from diabetes mellitus and receiving insulin-semilente for correction of hyperglycemia. 10 days ago, he began treatment of hypertensive disease with anaprilinum. In an hour after drug intake, hypoglycemic coma is developed in the patient. What is the mechanism of this complication development?

A. Increase of insulin-semilente bioavailability.

B. Inhibition of glycogenolysis.

C. Increase of insulin-semilente half-life.

D. Decrease of glucose absorption.

E. Decrease of glucagon release.

55. A 60-year-old patient is suffering from diabetes mellitus and receiving insulin semilente for correction of hyperglycemia. 10 days ago, he began treatment of hypertensive disease with anaprilinum. In an hour after drug intake, the patient felt weakness, dizziness, drop of blood pressure. The patient lost consciousness in several minutes. Which pathological condition is developed in the patient?

A. Acute vessels insufficiency.

B. Hyperglycemic coma.

C. Hypoglycemic coma.

D. Acute disturbance of cerebral blood flow.

E. Cardiogenic shock.

56. A 60-year-old patient is suffering from diabetes mellitus and receiving insulin-semilente for correction of hyperglycemia. 10 days ago, he began treatment of hypertensive disease with anaprilinum. In an hour after drug intake, the patient felt weakness, dizziness, drop of blood pressure. The patient lost consciousness in several minutes. Which drug should be administered to the patient for primary care?

A. Bemegride.

B. Glucose.

C. Noradrenaline.

D. Sodium bicarbonate.

E. Insulin.

57. A woman who for some time has been treated for chronic polyarthritis complains of blood pressure increase, redistribution of fat, and menstrual disturbances. Choose the drug which is taken by woman.

A. Beclomethasone.

B. Indomethacin.

C. Butadione.

D. Prednisolone.

E. Synaflan.

58. A patient with recurrent allergic dermatitis needs the appointment of glucocorticoid. Choose the drug which has local influence upon the skin without systemic side effects.

A. Triamcinolone.

B. Prednisolone.

C. Hydrocortisone.

D. Dexamethasone.

E. Synaflan.

59. Hypoglycemic coma is developed in patient owing to overdose of insulin. Which drug should be administered to its elimination?

A. Glucose.

B. Lente insulin.

C. Prednisolone.

D. Glucagon.

E. Tolbutamide.

60. A 60-year-old woman during long time uses dexamethasone for treatment of arthritis. What is the mechanism of anti-inflammatory effect of this drug?

A. Blockage of folate reductase.

B. Blockage of cyclooxygenase-1.

C. Blockage of cyclooxygenase-2.

D. Blockage of phospholipase A_2.

E. Blockage of folate synthetase.

61. A 9-year-old child with multiple caries receives calcitonin. Which therapeutic effect of drug is used in this case?

A. Increase of saliva pH.

B. Inhibition of glycolysis.

C. Activation of osteoblasts.

D. Increase of fluor concentration in oral cavity.

E. Decrease of glucose concentration on oral cavity.

62. A patient with diabetes mellitus receives injections of thiamine for correction of metabolic acidosis. What is the mechanism of therapeutic action of vitamin B_1 in this case?

A. Increase of adrenaline synthesis.

B. Activation of adenylyl cyclase.

C. Blockage of phosphodiesterase.

D. Increase of acetylcholine synthesis.

E. Activation of the Krebs cycle dehydrogenases.

63. Owing to sudden cessation of glucocorticoid intake, the following complications develop in patient: aggravation of rheumatoid arthritis, decrease of blood pressure, and weakness. What is the cause of these complications?

A. Cumulation.

B. Insufficiency of adrenal cortex.

C. Sensibilisation.

D. Hypersecretion of adrenocorticotropin.

E. Development of tolerance.

64. A 25-year-old pregnant woman is admitted to the pregnancy pathology department with threatened abortion. Which drug should be prescribed to the woman?

A. Synoestrol.

B. Folliculin.

C. Progesterone.

D. Estradiol.

E. Retabolil.

65. A patient after subtotal resection of thyroid gland receives drug of substitute therapy. What is the name of this drug?

A. Potassium perchlorate.

B. Potassium iodide.

C. Mercazolil.

D. Thyroxine.

E. Antistrumin.

66. A 65-year-old patient with non-insulin-dependent diabetes mellitus receives glibenclamide perorally. What is the mechanism of glibenclamide action?

A. Drug inhibits degradation of polysaccharides.

B. Drug inhibits gluconeogenesis in liver.

C. Drug increases the use of glucose by peripheral tissues.

D. Drug suppresses absorption of glucose in intestine.

E. Drug stimulates the release of insulin by beta-cells of pancreas.

67. Pituitrin was administered to woman with weak labor. Indicate hormones which are contained in this drug?

A. Vasopressin and progesterone.

B. Oxytocin and vasopressin.

C. Oxytocin and progesterone.

D. Vasopressin and estradiol.

E. Oxytocin and estradiol.

68. A 47-year-old patient with thyrotoxicosis receives drug which inhibits the synthesis of thyroid hormones in thyroid gland. Choose this drug.

A. Radioactive iodine.

B. Diiodotyrosine.

C. Mercazolil.

D. Thyroidin.

E. Potassium iodide.

69. A 45-year-old patient complains of constant thirst, marked polyuria. The glucose level in plasma is 5 mmol/L. There is no glucose in urine. Which drug should be prescribed for treatment of this patient?

A. Prednisolone.

B. Adiurecrinum.

C. Desoxycorticosterone.

D. Hydrocortisone.

E. Insulin.

ANTIALLERGIC DRUGS

Allergy is an immunologic reaction caused by the action of the antigen, which is accompanied by different functional and structural disorders in body tissues.

Both humoral and cell-mediated immunity participate in allergic reactions.

Humoral immunity is directed against extracellular antigens. Five types of antibodies (immunoglobulins) participate in humoral immunity: IgG, IgM, IgA, IgD, and IgE. These immunoglobulins are synthesized by plasmocytes (B-lymphocytes transformed under antigen influence).

Cell-mediated immunity is directed against intracellular and fungal infections, cancer cells, and intracellular parasites. Cell-mediated immunity is closely associated with T-lymphocytes. T-lymphocytes are devided into T-killers (kill cells which bind with antibodies), T-helpers (cells with cooperative function), T-producents of lymphokines, and T-suppressors (participate in formation of immune tolerance).

Monocytes and macrophages also produce biologically active substances regulating and increasing immunity. These substances are

named cytokines. Cytokines influence inflammation and exert antibacterial, antitumoral, and antiproliferative effects.

Allergic reactions are divided into allergic reactions of an immediate type and allergic reactions of a delayed type.

There are 3 stages in pathogenesis of allergic reactions: immunological, pathochemical, and pathophysiological.

Immunological stage develops during the initial penetration of an allergen in the body and its interaction with antibodies and T-lymphocytes (at repeated penetration in the body). During this stage, sensitization of the body occurs.

Pathochemical stage is a period from an allergen interaction with immunity effectors to synthesis of biologically active substances – mediators of allergic reactions.

Pathophysiological stage develops when mediators act on body cells and tissues that is accompanied by development of structural and functional disorders with corresponding clinical symptoms.

To treat allergic reactions, it is necessary to determine allergen initially. Removal of the allergen gives the best result. If it is impossible, the specific hyposensitization is used. With this end in view, small doses of allergen are administered in the body that leads to decrease of body sensitivity to this allergen.

Antiallergic drugs are used fot pathogenetic treatment of allergic reactions. These drugs are classified as follows.

1. Drugs which are used to treat immediate-type allergy.

1.1. Glucocorticoids: *hydrocortisone, prednisolone, methylprednisolone,* and *dexamethasone*.

1.2. Antagonists of H_1-histamine receptors: *diprazinum, diphenhydramine (Dimedrol), quifenadine (Phencarol), diazolinum, chloropyramine (Suprastin),* and *loratadine (Claritin),* etc.

1.3. Stabilizers of membranes of tissue basophils: *cromolyn sodium (Intal)* and *ketotifen (Zaditen)*.

1.4. Inhibitors of leukotriene receptors: *zafirlukast (Accolate), montelukast (Singulair),* etc.

1.5. 5-Lipoxygenase inhibitors: *zileuton*.

1.6. Inhibitors of fibrinolysis: *aminocaproic acid*, etc.

1.7. Drugs decreasing the manifestations of allergic reactions:

– adrenomimetics: *adrenaline, ephedrine, mesatonum*, etc.;

– antagonists of M-cholinergic receptors: *atropine, metacinium*, etc;

– myotropic spasmolytics: *euphyllin*, etc;

– steroid and non-steroid anti-inflammatory drugs.

2. Drugs used to treat delayed-type allergy.

2.1. Immunosuppressive drugs: cytostatic agents, glucocorticoids, and "minor" immunosuppressants.

2.2. Drugs reducing damage of tissues: steroid and non-steroid anti-inflammatory agents.

Drugs Used to Treat Immediate-Type Allergy

Glucocorticoids

Glucocrticoids are *hydrocortisone, prednisolone, dexamethasone, methylprednisolone,* etc. These drugs inhibit protein synthesis in a body and, due to this, decrease synthesis of immunoglobulins that leads to decrease of formation of antigen-antibody complex.

Besides, glucocorticoids block F_c-receptors of basophils membranes that results in reduction of phospholipase A_2 activity and decrease of calcium entrance in basophils. Due to this, the secretion of histamine, serotonin, SRS-A (slow-reacting substance of anaphylaxis) is reduced. Also, glucocorticoids sensibilize adrenergic receptors to catecholamines.

Prednisolone, prednisone, and methylprednisolone are most commonly used glucocorticoids in clinical practice. Other drugs are used less often due to serious side effects. Even though triamcinolone has little influence upon water-salt balance, this agent causes weight loss, weakness, muscular atrophy, ulcer disease, and rush of blood to the head. Dexamethasone causes significant water retention and circulatory failure.

Most often, glucocorticoids are prescribed for oral intake. Its effect lasts 6–8 hours. At intramuscular or intravenous administration, drug effect lasts 2–3 hours. Presently, prolonged medicinal forms of betamethasone (Celestone) and triamcinolone are used for oral and parenteral administration. Also, inhaled forms of betamethasone are used treat moderate bronchial asthma. Herewith, the drug exerts mainly local influence upon bronchi with low frequency of side effects.

Glucocorticoids are used to treat the following immediate-type allergic reactions:

– status asthmaticus (prednisolone intravenously);

– anaphylactic shock (prednisolone with adrenaline intravenously);

– moderate bronchial asthma (drugs administered in inhalations).

Histamine H_1-Receptor Antagonists

Nowadays, 4 types of histamine receptors are known. Stimulation of histamine H_1-receptors leads to contraction of smooth muscles of internal organs, increased vascular permeability, tissue oedema, pain, and itch. Stimulation of histamine H_2-receptors is accompanied by the increase of gastric secretion, vasorelaxation, and tachycardia. Stimulation of H_3-receptors results in contraction of smooth muscles of gastrointestinal tract and bronchi, increased vascular permeability, and activation of T-lymphocytes, neutrophils, and eosinophils.

Histamine H_1-receptor antagonists block H_1-receptors and reduce or eliminate the following effects of histamine: bronchoconstriction, intestinal spasms, uterine spasm, hypotension, increased vascular permeability, itch, tissue oedema, and erythema.

Histamine H_1-receptor antagonists are classified as follows.

– I generation: *diphenhydramine (Dimedrol), clemastine (Tavegyl), chloropyramine (Suprastin), mebhydrolin (Diazolin), promethazine (Diprazin, Pipolphen), quifenadine (Phencarol).*

– II generation: *terfenadine (Seldane), astemizole (Hismanal), loratadine (Claritin).*

– III generation: *levocetirizine, desloratadine, norastemizole.*

The drugs of II and III generations exert higher efficacy and selectivity, longer duration of action, and do not influence central nervous system.

Histamine H_1-receptor antagonists block only free histamine receptors. These drugs do not replace histamine binding with receptors. It is due to higher affinity of histamine to receptors in comparison with these drugs.

Histamine H_1-receptor antagonists are also characterized by some other pharmacological properties. Diprazin, Dimedrol, and Suprastin exhibit marked sedative and hypnotic influence on central nervous system. Besides, these drugs exert M-cholinoblocking activity. Also, Diprazin potentiates th effects of general anaesthetics, opioid analgesics, and local anaesthetics. Diprazin influences termoregulation and decreases the body temperature. Diprazin and Dimedrol exhibit local anaesthetic effect. Dimedrol blocks impulse transmission through vegetative ganglia that results to relaxation of smooth muscles of internal organs. Diprazin exerts α-adrenoblocking activity that decreases blood pressure, especially in case of intravenous administration. Diprazin, Dimedrol, and Suprastin exert direct moderate antispasmodic effect.

Histamine H_1-receptor antagonists are taken orally or administered intravenously and intramuscularly. In case of oral intake, the bioavailability of the I-generation drugs is about 40 %, because these drugs undergo metabolism at first pass through a liver. Bioavailability of II-generation drugs is above 90 %. A rate of binding with plasma proteins of histamine H_1-receptor antagonists is about 90 %. In oral intake, onset of drug effect is 20–40 minutes. Duration of action of I-generation drugs is 4–6 hours. These drugs are taken 3–4 times a day (except Tavegyl which is taken 2 times a day). Therapeutic concentration of II-generation drugs remains in a body up to 20 hours. These drugs are taken once a day.

Most drugs of I generation (except Diazolin and Phencarol) easily penetrate through blood-brain barrier. II-generation drugs practically do not penetrate central nervous system.

Histamine H_1-receptor antagonists andergo hepatic metabolism by way of methylation. Main routes of drug excretion are kidneys and liver.

Therapeutic indications for histamine H_1-receptor antagonists are the following.

1. Allergic reactions of immediate type: urticaria, allergic rhinitis, angioedema, itch, and neurodermatitis.
2. Insomnia (Dimedrol and Diprazin are mainly used).
3. Premedication (Diprazin and Dimedrol).
4. Motion sickness (Dimedrol).
5. Complex treatment of bronchial asthma, anaphylactic shock, and acute pulmonary oedema.
6. Traumas of skin and soft tissues (to prevent histamine effects).
7. Potentiation of analgesic effects of non-steroidal anti-inflammatory drugs (Dimedrol).

Most often side effects of histamine H_1-receptors antagonists include dry mouth, constipation, tachycardia, accommodation disorders, drowsiness, and decreased attention span. These effects develop due to M-cholinoblocking and sedative activity of these drugs. Besides, Dimedrol exerts ganglion blocking activity and can lower blood pressure. Diprazin also lowers blood pressure due to blockage of α-adrenergic receptors. Some drugs (especially Diprazin and Diazolin) irritate mucous membrane of the stomach that results in dispepsia. Dimedrol increases seizure brain activity; therefore, the drug can provoke the convulsions in patients with epilepsy and encephalopathy. Drugs with sedative effect should be avoided in patients whose profession requires attention and fast psychomotor reactions.

Stabilizers of Membranes of Tissue Basophils

This group is represented by *cromolyn sodium (Intal)* and *ketotifen (Zaditen).* These drugs block calcium entering tissue basophils that results in histamine release inhibition. These drugs exert only preventive anti-allergic effect.

Cromolyn sodium is administered by inhalation to treat bronchial asthma. For inhalation, a special capsule with finest powder of cromolyn sodium is placed in the Spinhaler™. Therapeutic effect develops gradually: in 2–4 weeks of everyday inhalations 4 times a day. Also, cromolyn sodium is used in the treatment for allergic rhinitis, conjunctivitis, and enteritis.

Ketotifen also exhibits moderate ability to block histamine H_1-receptors. The drug is taken orally 2 times a day. Ketotifen is readily absorbed from gastrointestinal tract. Therapeutic indications for ketotifen are bronchial asthma, allergic rhinitis, conjunctivitis, dermatitis, and alimentary allergy. Stable therapeutic effect develops in 10–12 weeks. Side effects develop seldom and include drowsiness and increased appetite.

It should be noticed that phosphodiesterase inhibitors (euphyllin), glucocorticoids (prednisolone, beclomethasone, etc.), β_2-adrenomimetics (salbutamol, fenoterol, etc.) are groups of drugs which also inhibit histamine release from basophils.

Leukotriene Receptor Antagonists

Zafirlukast (Accolate), and *montelukast (Singulair)* are drugs which block leukotriene C_4, D_4, and E_4 $CysLT_1$-receptors.

Zafirlukast reduces bronchoconstriction, decreases the vascular permeability, and inhibits the bronchial secretion. The drug is taken orally in dose 0.02 g twice a day to prevent bronchial asthma attacks. Stable therapeutic effect develops in 1 week after initiation of therapy.

Montelukast acts longer and is taken once a day.

5-Lipoxygenase Inhibitors

Zileuton blocks 5-lipoxygenase – enzyme catalyzing synthesis of leukotrienes from arachidonic acid. The drug is used to treat bronchial asthma. Zileuton is especially effective in aspirin-induced asthma, which is a complication of non-steroid anti-inflammatory drugs.

Drugs Reducing Manifestations of Allergic Reactions

Variety of chemical messengers of allergy and deficiency of their antagonists require to use functional antagonists of allergy mediators in the treatment of allergic reactions. A choice of antagonists is determinated by character of allergic reaction. Usually, functional antagonists of allergy mediatirs, antihistaminergic drugs, and drugs of basic therapy inhibiting release of mediators are used simultaneously.

At muscle spasms of the gastrointestinal tract (allergic enteritis, colitis, etc.), antagonists of M-cholinergic receptors (*atropine*, etc.) and myotropic antispasmodic drugs (*No-spa*, etc.) are drugs of choice. *Loperamide (Imodium)* and *bismuth subsalicylate (Pepto-Bismol)* are used to cessate diarrhea. Also, H_1-histamine blockers (*dimedrolum*, etc.) are used in the treatment for allergic enteritis and colitis.

At bronchial asthma, β-adrenomimetics (*isadrinum, salbutamol*, etc.), antagonists of M-cholinergic receptors (*ipratropium bromide (Atrovent), traventol, metacinium*, etc.), myotropic antispasmodic drugs (*euphyllinum*, etc.), glucocorticoids (*prednisolone, beclomethasone*, etc.), and stabilizers of the basophile cell membranes (*cromolyn sodium, ketotifen*, etc.) are used.

At cutaneous manifestations of allergy, histamine H_1-receptor antagonists are drugs of choice. Glucocrticoids are used in the treatment for generalized severe cutaneous manifestations. Besides, non-steroid anti-inflammatory drugs are applied topically. Antibacterial and antifungal drugs are prescribed if allergy is aggraveted by bacterial or fungal infection.

Local α-adrenomimetics (*naphthyzinum*, etc.) and histamine H_1-receptor antagonists are used in the treatment for allergic rhinitis. To prevent allergic rhinitis, stabilizers of the basophile cell membranes are used.

Nowadays, co-formulated drugs containing H_1-histamine receptor antagonists and pseudoephedrine are approved in the treatment for allergic rhinitis, laryngitis, and other allergic diseases of respiratory tract. *Clarinase* is a representative of such drugs. Pseudoephedrine is an indirect adrenomimetic. The drug causes vascular spasm due to stimulation of α-adrenergic receptors. It is accompanied by reduced swelling of respiratory mucous membrane. Pseudoephedrine has insignificant influence upon heart rate, blood pressure, and central nervous system.

Anaphylactic shock is a most dangerous immediate-type allergic reaction. Therapy of anaphylactic shock is directed to immediate elimination of cardiovascular collapse, respiratory disorders, hypovolemia, and convulsions. *Adrenaline* is a drug of choice to treat anaphylactic shock. About 0.3–0.5 ml 0.1 % adrenaline solution is administered subcutaneously or intramuscularly with intervals of 5–15 minutes under blood pressure control. Maximum dose of adrenaline is 2 ml. Adrenaline is an antagonist of different chemical messengers of anaphylaxis influencing smooth muscles. Besides, intravenous drop-by-drop administration of *dopamine* or *noradrenaline* with isotonic sodium chloride (glucose) solution is performed. Large-dose glucocorticoid (*prednisolone*, up to 100 mg), *calcium chloride*, and histamine H_1-receptor antagonist (*dimedrolum*) are also administered. If necessary, *diazepam*, *strophanthin*, and *furosemide* are prescribed. Mortality due to anaphylactic shock is within 10–60 %. Anaphylactic shock recurs in 12–15 % patients due to retaining of antigen in the body. Therefore, close monitoring of patient condition is necessary for several days.

Drugs Used to Treat Delayed-Type Allergy

Immunosuppressive Drugs

Immunosuppressive drugs are divided info the following groups.

1. Cytostatics: *cyclosporine, azathioprine, methotrexate, mercaptopurine*, etc.

2. Glucocrticoids: *prednisolone, methylprednisolone, dexamethazone, beclomethazone,* etc.

3. "Minor" immunosuppressants: *chloroquine,* gold-containing drugs *(auranofin, aurotioprol, sodium aurothiomalate (Myokrisin, Tauredon), penisillamine.*

Immunosuppressive drugs are used for pathogenetic therapy of severe manifestations of delayed hypersensitivity reactions. Mainly, these drugs are used to treat rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus, periarteritis nodosa, scleroderma, etc.), immune destruction of central nervous system, kidneys, and other autoimmune diseases. Immunosuppressive drugs are also used to inhibit graft rejection.

Lymphocytes play a major role in delayed hypersensitivity. Due to many receptors, lymphocytes recognize antigens and provide the specific reaction of the immune system. In this process, of great importance is interleukin-1 which is produced by monocytes-macrophages (cells which perform phagocytosis and antigen processing). Interleukin-1 activates T-helpers. Activated T-helpers produce specific cytokines – lymphokines, such as interleukin-2 (main mediator of the immune system regulating all phases of immune response), γ-interferon, etc. Interleukin-2 controls proliferation of T-killers, T-suppressors, and T-helpers. Besides, interleukin-2 promotes proliferation of B-lymphocytes producing different types of antibodies (immunoglobulins M, G, A, D, E). Further interaction of immunoglobulins with antigens results in autoimmune diseases.

The basis of immunosuppressants' efficacy is their ability to influence the key stages of the immune response.

Cytostatics

This group is represented by such drugs as *cyclosporine, tacrolimus, azathioprine, methotrexate, mercaptopurine, cyclophosphamide,* etc. Cytostatics are used in the treatment for severe forms of rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune diseases in cases when other drugs are ineffective. Also, these drugs are used to inhibit graft rejection.

Cyclosporine is an antibiotic consisting of 11 amino acids. Cyclosporine inhibits peptide synthesis and proliferation of T- and B-lymphocytes. Peculiarity of the drug is its ability to reversible selective inhibition of early stages of cellular immune response. Cyclosporine inhibits ability of T-helpers to produce interleukin-2 and γ-interferon. It results in a reduction of killer T-cell formation. In contrast with other cytostatics, cyclosporine does not inhibit hemopoiesis and proliferation of gastrointestinal mucosa. Cyclosporine is mainly used to inhibit graft rejection (after transplantation of bone marrow, kidneys, liver, heart, etc.). Besides, the drug is used in the treatment for autoimmune diseases. It should be noticed that cyclosporine exerts marked nephrotoxicity and can inhibit hepatic function. Besides, cyclosporine can cause infertility, hair loss, nausea, and vomiting.

Tacrolimus (Prograf) is an antibiotic of macrolide group. The drug inhibits activation of T-lymphocytes and reduces interleukin-2 production. Immunodepressive activity of tacrolimus is 100 times more than those of cyclosporine. The drug is used to inhibit graft rejection. Side effects of tacrolimus are nephrotoxicity, neurotoxicity, hypertension, dyspeptic disorders, etc.

The properties of *azathioprine* are similar to mercaptopurine, but this drug is less toxic. In a body, azathioprine is converted into 6-mercaptopurine. This metabolite inhibits the proliferation of T-lymphocytes. Therapeutic indications for azathioprine are autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.) and inhibition of graft rejection. Azathioprine inhibits the function of bone marrow that results in leukopenia,

anemia, and thrombocytopenia. Dyspeptic disorders and toxic damage of liver are also possible.

Cyclophosphamide, methotrexate, and *mercaptopurine* are also used as immunosuppressive drugs. These agents block cellular proliferation of cells, including B- and T-lymphocytes, and slow down the protein synthesis. The drugs exert different mechanisms of action. Thus, cyclophosphamide crosslinks DNA helices and affects the normal DNA structure that results in disorders of replication and cell division. Methotrexate is folic acid antagonist and affects synthesis of purines and pyrimidines. Mercaptopurine is a competitor of natural purine nucleotides.

Serious disadvantages of cytostatics are:

– cytotoxic effect concerning tissues with high rate of physiological regeneration (inhibition of hemopoiesis with anemia, leukopenia, and thrombocytopenia; slowdown of regeneration of gastrointestinal mucosa, etc.);

– reduction of body resistance to viruses, bacteria, and fungi;

– nephro- and hepatotoxicity.

It is advisable to combine cytostatic therapy with intake of nonsteroid and steroid anti-inflammatory drugs.

Glucocorticoids

Glucocorticoids (*prednisolone, dexamethazone, triamcinolone*, etc.) exert marked immunosuppressive effect. These drugs inhibit proliferation of T- and B-lymphocytes. Glucocrticoids influence macrophages and violate antigen recognition. Also, glucocorticoids inhibit production of interleukin-2, γ-interferon, and factor inhibiting migration of macrophages. Glucocorticoids suppress cytotoxicity of T-killers. High doses of glucocorticoids inhibit immunoglobulins synthesis by plasma cells. Besides, glucocorticoids exert fast and marked anti-inflammatory effect.

Combination of immunosuppressive and anti-inflammatory effects promotes the high efficacy of glucocorticoids in therapy of different autoimmune diseases. Glucocrticoids are used in the

treatment for rheumatoid diseases, other autoimmune processes, and to inhibit graft rejection.

After kidney transplantation, *muromonab-CD3 (Orthoclone OKT3)* is used to prevent graft rejection. This drug is preparation of monoclonal antibodies which selectively inhibit T-lymphocytes.

"Minor" Immunosuppressants

This group includes such drugs as *chloroquine*, gold preparations *(auranofin, aurotioprol, sodium aurothiomalate (Myokrisin, Tauredon)*, etc.), and *penicillamine*. "Minor" immunodeppressants are drugs for baseline therapy of collagenosis. Most commonly, these drugs are used in treatment of such diseases as rheumatoid arthritis, systemic lupus erythematosus, etc. The drugs inhibit cellular and humoral immunity and suppress inflamation (mainly in proliferation phase).

Chloroquine stabilizes lysosomal and cellular membranes, inhibits phagocytosis, decreases synthesis of interleukines 1 and 2, inhibits proliferation of T-lymphocytes and cells of connective tissues in rheumatoid lesions, and destroys collagen synthesis. Anti-inflammatory activity of chloroquine is less than the those of penicillamine and gold preparations. But chloroquine exerts low toxicity. Drug effect develops in 10–12 weeks after the initiation of therapy.

Auranofin, aurotioprol, sodium aurothiomalate (Myokrisin, Tauredon), etc. are gold-containing preparations. These drugs are accumulated in rheumatoid lesions of joints, inhibit macrophagal function, and reduce blood concentrations of immunoglobulins and rheumatoid factor that results in the decrease of joint damage. Aurotioprol is administered intramuscularly 1 time in 2–5 days. Its effect develops in 6 months after therapy initiation. Gold preparations are characterized by high nephro- and hematotoxicity.

Penicillamine interacts with rheumatoid factor and destroys it. Besides, the drug affects collagen maturation and suppresses proliferation of T-lymphocytes. Penicillamine forms the complexes

with bivalent metals. Thus, complexation with copper is accompanied by neutralization of active oxygen radicals which support the autoimmune processes and inflammation. Penicillamine is taken orally according to scheme. The drug efficacy may be estimated within 9–15 months after initiation of therapy. Penicillamine is toxic drug which can cause nausea, vomiting, diarrhea, hypertermia, renal dysfunction, skin redness, etc.

IMMUNOMODULATORS

Immunomodulators are drugs which normalize cellular and humoral immunity. Drugs are used in the treatment for diseases developing due to immune dysfunction: immunodeficiency states, chronic infections, and oncological diseases.

Immunomodulators are classified as follows.

1. Preparations of thymus: *thymalin, thymoptin, tactivinum, vilosenum.*

2. Synthetic drugs: *levamisole, dibazolum (bendazole), pentoxyl, methyluracil, bemethyl.*

3. Agents of microbial origin: *Ribomunyl, bronchomunal, pyrogenalum, prodigiozan, BCG vaccine, poludanum, licopid, Ismigen, IRS-19.*

4. Cytokines (preparations of lymphokines that are produced by lymphocytes): *interferon α, interferon α-2a, interferon α-2b, interferon β, interferon β-1b, interferon γ, interleukin-1 (betaleukin), interleukin-2 (proleukin), reaferon, roncoleukin.*

5. Drugs of plant origin: *preparations of echinacea, ginseng, eleutherococcus,* etc.

Thymus produces about 8–10 hormones promoting maturation of lymphocytes and regulation of different stages of immune response. *Thymalin, thymoptin, tactivinum, vilosenum,* etc. are extracted from thymus and contain several thymus hormones. Thymus preparations restore the activity of the immune system at its inhibition or disfunction. These drugs activate both humoral and

cellular immunity, phagocytosis, tissue regeneration, and hemopoiesis.

Thymalin and tactivinum are used in the treatment for indolent viral, bacterial, and fungal infections; burn disease; sores; bedsores; radiation damage, etc. Thymalin is administered intramuscularly during 5–20 days, tactivinum – subcutaneously. Vilosenum is applied intranasally to treat rhinitis and sinusitis.

Synthetic drugs influence membrane receptors of lymphocytes which are sensitive to neurohumoral regulation including influence of thymus hormones.

Levamisole increases the cell sensitivity to thymus hormones and stimulates cellular and humoral immunity and phagocytosis. Also, levamisole stimulates the proliferation of T-lymphocytes and production of interleukins and interferons. The drug is taken 1–2 times per week. The course of treatment lasts from 2–3 weeks up to 1 year. Toxicity of levamisole is high. Levamisole therapy is accompanied by gastrointestinal dysfunction, agranulocytosis, insomnia, etc.

Dibazolum (bendazole) activates nonspecific body resistance and phagocytosis, increases synthesis of antibodies, interferons, and other mediators of immunity. Its immunomodulating effect develops gradually. The drug is used to prevent infectious diseases.

Bemethyl activates protein synthesis and energy production in tissues including cells of immune system. The drug increases synthesis of antibodies and stimulates T-lymphocytes activity and macrophagal function. Bemethyl is used in the treatment for viral hepatitis, recurrent respiratory infections, recurrent erysipelas, pyoderma, etc.

Pentoxyl and *methyluracil* are widely used to accelerate wound healing, to stimulate cellular or humoral immunity and leukopoiesis.

Licopid is a synthetic immunomodulator. Molecules of licopid contains glucosaminyl-muramyl-dipeptide (GMDP). GMDP is the component of almost all bacterial cell walls. Therefore, licopid stimulates phagocytosis, activates T- and B-lymphocytes, increases the synthesis of interferons, interleukins, the tumor necrosis factor,

antibodies, and other mediators of immunity. Licopid is intended for treatment of chronic infectious diseases.

Prodigiozan is the lipopolysaccharide complex obtained from bacteria. *Ribomunyl* contains fragments of bacterial membranes. Both drugs stimulate cellular and humoral immunity, increase synthesis of interferons and nonspecific organism resistanse. Drugs are used to treat infectious diseases (sinusitis, dysentery, hepatitis B, sepsis, pneumonia, bronchitis, rhinitis, osteomyelitis, etc.) in patients with immunodeficiency. Prodigiozan is administered intramuscularly 1 time for 3–5 days. Ribomunyl is taken orally according to a dosing regimen.

BCG vaccine is used to prevent tuberculosis. Besides, it is used in the complex treatment for malignant tumours. BCG vaccine stimulates macrophages and T-lymphocytes. Therapeutic effect of BCG vaccine is observed in myeloid leukemia, some lymphoma, cancer of intestine and mammary gland, bladder, etc.

Bronchomunal is a hydrolysate of 8 microbial species most common causative agents of respiratory infections. Bronchomunal stimulates the activity of macrophages, and T-helpers. Besides, the drug increases concentration of immunoglobulin A and synthesis of interleukin-2 and γ-interferon. Bronchomunal is used to prevent and treat respiratory infectious.

Interferons are used as antiviral drugs. γ-Interferon exerts less influence upon viral infections, but higher influence upon deep regulation of immune response. γ-Interferon inhibits phagocytosis, stimulates activity of T-killers, and modulates the antibodies' synthesis. γ-Interferon is used in the treatment for tumoral diseases, chronic viral and fungal infections, rheumatoid arthritis, and other collagenosis.

Betaleukin (interleukin-1β) is intended to treat leukopenia, thrombocytopenia, and lymphopenia in oncological patients after intensive chemo- and radiation therapy.

Roncoleukin is recombinant interleukin-2. The drug is used in the treatment for chlamidiasis, malignant tumors, pyoinflammatory diseases, bacterial, viral and fungal infections.

Immunomodulators of plant origin stimulate cellular immunity and phagocytosis, promote release of interferons, and increase nonspecific body resistance. These drugs are used to prevent and treat respiratory infections, influenza, etc.

Table 13 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Acidum acetylsalicylicum	Orally 0.25–1.0 g 3–4 times a day	Tablets 0.1; 0.25 or 0.5 g
Analginum	Orally 0.25–0.5 g 2–3 times a day; intramuscularly and intravenously 0.25–0.5 g 2–3 times a day	Tablets 0.5 g; ampoules 1 ml or 2 ml of 25 % or 50 % solution
Butadionum	Orally 0.1–0.15 g 2–4 times a day; externally 5 % ointment	Tablets 0.15 g; ointment 5 % – 20 g
Celecoxibum	Orally 0.1–0.2 g 1–2 times daily	Capsules 0.1 or 0.2 g
Ibuprofenum	Orally 0.2 g 3–4 times daily	Coated tablets 0.2 g
Diclofenac-natrium	Orally 0.025–0.05 g 1–3 times a day; intramuscularly 0.075 g 1 time a day	Coated tablets 0.025 g; ampoules 3 ml of 2.5 % solution
Prednisolonum	Orally 0.005–0.01 g; externally 0.5 % ointment	Tablets 0.005 g; ointment 0.5 % – 10.0 or 20.0 g
Prednisoloni hemisuccinas	Intravenously or intramuscularly 0.05–0.2 g 2–6 times a day	Ampoules 0.025 g of powder for injection
Dexamethasonum	Orally 0.000 5–0.001 g 2–3 times a day	Tablets 0.000 5 g
Cromolinum-natrium	For inhalation 1 capsule 4 times a day	Capsules 0.02 g
Dimedrolum	Orally 0.03–0.05 g 1–3 times a day; intramuscularly or intravenously 0.01–0.05 g	Tablets 0.03 or 0.05 g; ampoules 1 ml of 1 % solution

Continuation of the table 13

Drug name (Latin)	Single dose and route of administration	Drug product
Diprazinum	Orally 0.025 g 2–3 times a day; intramuscularly or intravenously 0.05–0.25 g	Coated tablets 0.025 g; ampoules 2 ml of 2.5 % solution
Suprastinum	Orally 0.025 g 2–3 times a day; intramuscularly or intravenously 0.02–0.04 g	Tablets 0.025 g; ampoules 1 ml of 2 % solution
Thymalinum	Intramuscularly 0.005–0.03 g 1 time a day	Vials 0.01 g of powder for injection
Euphyllinum	Orally 0.25 g 2–3 times a day; intramuscularly 0.24–0.36 g 1–3 times a day; intravenously slowly or intravenously drop-by-drop 0.12–0.24 g	Tablets 0.25 g; ampoules 5 ml of 2 % solution
Adrenalini hydrochloridum	Subcutaneously, intramuscularly or intravenously 0.0005 g	Ampoules 1 ml of 0.1 % solution

Step 1. Tasks for Self-Control
Antiallergic and Immunotropic Drugs

1. A patient has urticaria, which is treated with dimedrol. Which element of allergy pathogenesis is the therapeutic effect of dimedrol connected with?

A. Activation of β-lymphocytes.

B. Interaction of histamine with receptors in organs.

C. Formation of the antigen-antibody complex.

D. Synthesis of immunoglobulins.

E. Histamine secration.

2. For treatment of joints arthritis a physician prescribed a drug which belongs to nonsteroid anti-inflammatory medicines. It mainly

influences cyclooxygenase-2. It has no irritative influence on the mucous coat of the digestive system. What drug is it?

A. Ibuprofen.

B. Indomethacin.

C. Diclofenac sodium.

D. Acetylsalicylic acid.

E. Celecoxib.

3. Second generation antihistaminic drug is a derivative of piperidine, taken once a day. It has no M-anticholinergic and adrenergic blocking effects. It shows antiallergenic, antiexudative, antipruritic action. What drug is this?

A. Retinol acetate.

B. Dimedrol.

C. Loratadine.

D. Suprastin.

E. Diazolin.

4. A 45-year-old woman suffers from allergic seasonal coryza caused by the ambrosia blossoming. What adipose cells group stabilizer medicine can be used for prevention of this disease?

A. Diazolin.

B. Dimedrol.

C. Phencarol.

D. Ketotifen.

E. Tavegyl.

5. A patient with continuous bronchopneumonia was admitted to the therapeutic department. Antibiotic therapy didn't give much effect. What drug for improvement of immune state should be added to the complex treatment of this patient?

A. Analginum.

B. Benadryl.

C. Sulfocamphocaine.

D. Timaline.

E. Paracetamol.

6. Signs of gastropathy develop in patient with rheumatoid arthritis who was treated with indomethacin. What activity of the drug does cause this complication?

A. Antihistamine.

B. Anti-cyclooxygenase.

C. Local irritating.

D. Antikinine.

E. Antiserotonin.

7. Aspirin has anti-inflammatory effect due to inhibition of the cyclooxygenase activity. Level of what biological active compounds will decrease?

A. Biogenic amines.

B. Catecholamines.

C. Prostaglandins.

D. Iodinethyronyns.

E. Leukotrienes.

8. A 52-year-old patient with bronchial asthma was treated with glucocorticoids. Fever reaction appeared as a result of postinjective abscess. The patient had subfebrile temperature, which didn't correspond to latitude and severity of inflammatory process. Why did the patient have low fever reaction?

A. Violation of heat-producing mechanisms.

B. Thermoregulation centre inhibition.

C. Violation of heat loss through lungs.

D. Inflammatory barrier formation in injection place.

E. Inhibited endogen pyrogens production.

9. A 40-year-old woman appealed to a doctor with a complaint of pain in the knee joints. During examination the doctor revealed swelling, reddening, hyperthermia in these joints area. Laboratory tests showed positive acute phase reactions. What drugs have to be used for treatment of the patient?

A. Anti-inflammatory agents of nonsteroid structure.

B. Opioid analgesics.

C. Antidepressants.

D. Antibiotics.

E. Sulfamides.

10. A 62-year-old man has been suffering from coxitis for a long time. A doctor prescribed him a new nonsteroid anti-inflammatory agent celecoxib. It improved the patient's state. What is the advantage of this drug?

A. Activation of phosphodiesterase.

B. Depression of phosphodiesterase.

C. Activation of adenylate cyclase.

D. Depression of cholineesterase.

E. Selective blockade of cyclooxygenase-2.

11. A patient with rheumatoid arthritis had been taking glucocorticosteroid during several weeks. Then he suddenly stopped taking this drug. What complication can occur in this case?

A. Formation of ulcers on the mucous coat of the stomach and duodenum.

B. Hypertension.

C. Withdrawal syndrome.

D. Exacerbation of chronic infection processes.

E. Hyperglycemia.

12. Allergic dermatitis produces itching, hypostasis, reddening, and insomnia. What drug is expedient for prescribing to the patient?

A. Natrii oxybutiras

B. Phenobarbital.

C. Nitrazepam.

D. Chloral hydrate.

E. Dimedrol.

13. A 30-year-old male, who works as a driver, suffers from allergic rhinitis which is aggravated during spring. The doctor has prescribed to him antihistamine drug with long duration of action (about 24 hours) and with insignificant sedative action. What drug was prescribed?

A. Loratadine.

B. Dimedrol.

C. Heparin.

D. Vicasolum.

E. Oxytocin.

14. Urticaria has developed in a 40-year-old female after the use of washing-up liquid. Simultaneously with local treatment, the dermatologist has recommended the antihistamine drug loratidine. What should be the frequency of loratidine administration?

A. 1 time per a week.

B. 2 times daily.

C. 4 times daily.

D. 1 time daily.

E. 1 time per 2 days.

15. A female has appealed to a doctor with complaints of nasal stuffiness, dacryagogue, weakness, and dizziness which arise in the period of ambrosia flowering. What antihistamine agent should be prescribed?

A. Bisacodyl.

B. Penicillin.

C. Loratadine.

D. Metoprolol.

E. Analginum.

16. The marked drowsiness has developed in female suffering from allergic dermatitis that uses certain antiallergic drug during a week. Indicate this drug.

A. Cromolyn sodium.

B. Essenciale.

C. Dimedrol.

D. Adrenaline hydrochloride.

E. Aminazine.

17. After penicillin administration, Quincke’s oedema has developed in a patient. What drug should be administered to the patient immediately?

A. Rifampicin.

B. Ascorbic acid.

C. No-spa.

D. Sulfacylum-natrium.

E. Prednisolone.

18. Antihistamine drug of the second generation was prescribed to the female suffering from allergic dermatitis. This drug does not render inhibitory influence upon the CNS. Identify this drug.

A. Loratadine.

B. Diazolin.

C. Tavegyl.

D. Dimedrol.

E. Ketotifen.

19. A student came to see a doctor and asked to administer him a drug for treatment of allergic rhinitis that occurs in the period of linden flowering. What drug may be used?

A. Propranolol.

B. Loratadine.

C. Losartan.

D. Noradrenaline hydrotartrate.

E. Ambroxol.

20. The quantity of phagocytes and antibody level decrease in patient during long-time treatment of pneumonia with aminoglycosides and sulfonamides. Which drug should be given to patient?

A. Mercazolil.

B. Coamidum.

C. Ferrum Lek.

D. Methyluracil.

E. Prednisolone.

21. The decrease of T-lymphocytes level is observed in a patient after ionizing radiation. Which drug should be prescribed to the patient?

A. Methyluracil.

B. Azathioprine.

C. Sodium nucleinate.

D. Ascorbic acid.

E. Thymalin.

22. A patient with aggravation of rheumatoid arthritis entered to hospital. Chronic hyperacidic gastritis is present in his anamnesis.

Choose drug, the administration of which is most appropriate in this case.

A. Butadione.

B. Indomethacin.

C. Ortofen (diclofenac-sodium).

D. Prednisolone.

E. Acetylsalicylic acid.

23. A patient suffers from seasonal allergic rhinitis owing to flowering poplar. Which drug should be prescribed to him for prevention of seasonal agravation of allergy?

A. Ranitidine.

B. Cromolyn sodium.

C. Ephedrine.

D. Prednisolone.

E. Diazolin.

24. A patient with acute rheumatism is treated with salicylates. After some time, he had insomnia. Doctor prescribes phenobarbital for treatment of insomnia. After several days of phenobarbital using, the anti-inflammatory effect of salicylates decreased. What is the cause of anti-iflammatory effect weakening?

A. Increase of salicylates elimination.

B. Chemical antagonism.

C. Pharmaceutical antagonism.

D. Inhibition of hepatic enzymes by phenobarbital.

E. Induction of hepatic enzymes by phenobarbital.

25. The cell-mediated immunity decreased in oncologic patient after radiation therapy. Choose immunomodulator for treatment of this patient.

A. Interferon.

B. Tactivinum.

C. Interferon-beta.

D. Reaferon.

E. Prodigiosanum.

26. Gastric bleeding developed in a 55-year-old patient on the 4-th day after the start of indomethacin intake. What is the cause of this complication?

A. Decrease of thromboxane synthesis.

B. Decrease of leukotriene synthesis.

C. Decrease of prostaglandin E1 synthesis.

D. Decrease of cyclic endoperoxides synthesis.

E. Decrease of prostagladin E_2 synthesis.

27. The following symptoms developed in a patient after long-time treatment with acetylsalicylic acid: headache, dizziness, sonitus, nausea, and epigastric pain. Which drug can cause these side effects?

A. Midantanum.

B. Acetylsalicylic acid.

C. Naphthyzinum.

D. Bromhexinum.

E. Vitamin C.

28. A 40-year-old woman has appealed to a doctor with complains of pain in joints. Laboratory exfmsnation has shown positive rheumatic test. Which group of drugs should be prescribed first of all?

A. Immunomodulators.

B. Opioid analgesics.

C. H1-histamine receptor blockers.

D. Glucocorticoids.

E. Nonsteroid anti-inflammatory drugs.

29. Indomethacin has been prescribed to a patient with rheumatism. But owing to aggravation of accompanied disease, the doctor has canceled this agent. Which disease is contraindication for indomethacin?

A. Hypertensive disease.

B. Angina pectoris.

C. Ulcer disease of stomach.

D. Diabetes mellitus.

E. Bronchitis.

30. A patient with rheumatoid arthritis suddenly stops the glucocorticoids intake after several weeks of treatment. Which complication can develop in this patient?

A. Acute adrenal insufficiency.

B. Hypertension.

C. Hyperglycaemia.

D. Aggravation of chronic infections.

E. Ulceration of stomach mucous membrane.

ANTI-ATHEROSCLEROTIC DRUGS

Anti-atherosclerotic (hypolipidemic) drugs are drugs of different chemical structure which reduce amount of cholesterol and triglycerides and their atherogenic carries in the blood. Due to this, hypolipidemic drugs slow down atherosclerosis progress and promote its regression. Majority of serious cardiovascular diseases are associated with atherosclerosis: ischemic heart diseases, myocardial infarction, ischemic stroke, encephalopathy, etc.

A basis of atherosclerosis progress is disorders of lipid metabolism leading to increase of cholesterol and triglycerides concentration on the blood. In plasma, lipids bind to proteins and form lipoproteins. There are the following groups of lipoproteins:

– chylomicrons;

– very-low-density lipoproteins (VLDL);

– intermediate-density lipoproteins (IDL);

– low-density lipoproteins (LDL);

– high-density lipoproteins (HDL).

VLDL, IDL, and LDL contain high concentrations of triglycerides and cholesterol and exert atherogenic properties.

Hyperlipoproteinemias are classified as follows.

1. Type I is characterized by increased blood concentration of chylomicrons.

2. Type II is characterized by increased blood concentrations of cholesterol, LDL, and VLDL.

3. Type III is characterized by increased blood concentrations of IDL and VLDL.

4. Type IV is characterized by increased blood concentration of VLDL.

5. Type V is characterized by increased blood concentration of chylomicrons and VLDL.

Hyperlipoproteinemias of I and V types are observed very seldom and occur in childhood. Risk of atherosclerosis at these types is insignificant.

Majority of hyperlipoproteinemias are primary, that is develops due to nutritive disturbances and sedentary lifestyle. Secondary hyperlipoproteinemias develop against the background of some diseases (diabetes melites, hypothyreosis, renal and hepatic diseases) or result from therapy by some drugs (β-adrenergic antagonists, diuretics, etc.).

Treatment of hyperlipoproteinemias is initiated with diet. If diet is ineffective, hypolipidemic drugs are prescribed to patient.

According to mechanism of action, hypolipidemic drugs are classified as follows.

1. Drugs decreasing blood concentration of cholesterol (LDL).

1.1. Inhibitors of cholesterol synthesis (statins): *lovastatin (Mevacor), fluvastatin (Lescol), mevastatin, simvastatin (Zocor), pravastatin (Lipostat), atorvastatin*.

1.2. Drugs increasing elimination of bile acids from the body (bile acid sequestrants): *cholestyramine* and *colestipol*.

1.3. Antioxidants: *probucol, vitamin E (tocopherol), vitamin C (ascorbic acid), vitamin* B_6 *(pyridoxine), β-carotin, microdoses of selenium*.

2. Drugs decreasing blood concentration of triglycerides (VLDL) – fibric acid derivatives (fibrates): *clofibrate, bezafibrate, gemfibrozil, fenofibrate*.

3. Drugs decreasing blood concentrations of both cholesterol (LDL) and triglycerides (VLDL).

3.1. Preparations of nicotinic acid: *nicotinic acid* and *acipimox*.

3.2. Drugs containing non-saturated fatty acids: *Moristerol, lipostabil, Essentiale, cod liver oil.*

3.3. Anticoagulants: *heparin.*

4. Direct vasoprotectors.

4.1. Endotheliotropic drugs: *parmidine, etamsylate, quercetin.*

4.2. Calcium antagonists: *verapamil, nifedipine.*

4.3. Antioxidants: *tocopherol, ascorbic acid, rutin, cysteine, methionine, glutamic acid.*

Drugs Decreasing Blood Concentration of Cholesterol

Cholesterol Synthesis Inhibitors (Statins)

Presently, this group is estimated as most effective for treatment of different types of hyperlipidemias including most severe forms. Mechanism of action of statins is associated with inhibition of 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It leads to slowdown of cholesterol synthesis at the stage of formation of mevalonic acid. Due to this, liver lacks about 60 % cholesterol which is essential for synthesis of bile acids. Deficiency of hepatic cholesterol is compensated by increased use of cholesterol and its ethers contained in food and increased utilization of cholesterol contained in vascular wall. Accumulation of cholesterol in vessels is cessated and atherosclerotic changes undergo regress. Amount of HDL, participating in cholesterol transport to the liver, is increased. Due to decrease of cholesterol synthesis, a density of LDL-receptors is increased. These receptors bind to LDL, VLDL, and IDL circulating in blood. It is importance, that statins do not block cholesterol synthesis in adrenal cortex and sex glands and do not inhibit synthesis of corticosteroids and sex hormones. Also, these drugs do not affect cholesterol synthesis in central nervous system.

Lovastatin, simvastatin, and *pravastatin* are natural substances produced by some species of fungi. Other drugs are synthetic agents.

Because cholesterol synthesis occurs mainly at night, statins are taken at evening while eating (absorption of drugs on an empty stomach is less). Maximum concentration in the blood is observed in 1.5 hours after drugs intake. A degree of binding with plasma proteins for statins is about 95 %. Statins andergo partial hepatic metabolism. Unchanged drugs and their metabolites are excreted by kidneys and liver. These drugs are well tolerated by patients. Therapeutic effect reach maximum in 4–6 weeks after initiation of treatment.

Side effects of statins are impaired hepatic function with elevation of blood level of transaminases, myopathy, dyspepsia, skin rash, photosensitization, anemia, and thrombocytopenia.

Statins are used to treat ischemic heart disease, II–IV types of hyperlipidemia, atherosclerosis of aorta, cerebral vessels, vessels of lower extremities, etc. Statins exert high efficacy at hereditary heterozygous form of hypercholesterinemia and non-hereditary (polygenic) hypercholesterinemia. Statins are not used to treat homozygous familial hyperlipoproteinemia because LDL-receptors are completely absent in these patients.

Therapy with statins is long-lasting and intake of minimal effective doses is preferable. A correction of initial dose is fulfilled in a month of therapy initiation with control of general cholesterol level (lower than 3.6 mmol/*l*).

Drugs Increasing Elimination of Bile Acids from the Body (Bile Acid Sequestrants)

This group is represented by enterosorbents and anion-exchange resins (*cholestyramine* and *colestipol*).

Molecules of these drugs contain many quaternary ammonium radicals and, therefore, bind anionic groups of bile acids with formation of non dissociable complexes excreted with feces. Due to their action, increased utilization of atherogenic lipoproteins (LDL and VLDL) is occurred in the liver and their synthesis is reduced. Simultaneously, hepatic synthesis of cholesterol, which is eccential for synthesis of bile acids, is increased.

Therapeutic effect is observed in 30–40 days after initiation of the drugs intake. Sequestrants of bile acids are mainly used to treat II type of hyperlipidemia. These drugs may be combined with other drugs in case of high hypercholesterolemia. Their effect develops in 1 month after initiation of therapy. Due to high safety, these drugs are used in pediatric practice.

Cholestyramine is taken orally as powder. Its dose is increased gradually from 3 g to 16–24 g daily for 1 month. The drug has very off-flavor taste and odour, therefore many patients swear off its intake. Side effects of cholestyramine are constipation, nausea, vomiting, diarrhea, and pancreatitis. Long-time drug intake can lead to deficiency of lipid-soluble vitamins.

Colestipol is better tolerated by patients. Its initial daily dose is 5–10 g. For 2–3 months, this dose is gradually increased up to 30 g. When therapeutic effect is reached, dose is gradually decreased to minimum. Colestipol is contraindicated for children under 6 years old. The drug violates intestinal absorption of medications and lipid soluble vitamins; therefore, their simultaneous intake is not recommended.

β-Sitosterol is natural steroid of plant origin which violate intestinal cholesterol absorption. The drug is used to treat II type hyperlipoproteinemia. The drug is well tolerated by patients, but its efficacy is low.

Presently, nonspecific sorbents of bile acids and cholesterol are widely used in medicine: vegetable fibres, pectins, cellulose, vegetable slimes and gums, some semisynthetic substances – sulfated derivatives of chitosan, polymannoses (long chain polysaccharides), Guar gum (guaran), activated lignin, etc. These drugs bind bile acids, cholesterol, bacterial toxins, and microelements. Their daily doses are about 20–50 g. Despite of these drugs are tolerated by patients well they have not self-sufficient value in the treatment of hyperlipoproteinemias.

Antioxidants

Peroxidation plays an importance role in pathogenesis of atherosclerosis. Before accumulation of vascular wall, ethers of cholesterol and triglycerides undergo oxidation by aggressive free oxygen radicals. Oxidation is occurred in case of deficiency of physiological antioxidants – vitamins E, A, and β-carotin. Peroxidation is also decelerated by vitamins C, B_6, microdoses of selenium, and vegetable flavonoids.

Antioxidants are divided into antioxidants of direct action and drugs of indirect action.

Antioxidants of direct action are tocopherol, polyphenols, ascorbic acid, "Aevit", ceruloplasmin, and superoxide dismutase. These drugs directly inhibit formation of free radicals. Vasoprotective action of these drugs is associated with their influence upon peroxidative, lipidemic, and thrombogenic mechanisms of atherogenesis. Due to deceleration of peroxidation of plasma lipoproteins, lipids, and phospholipids of vascular endothelium, these drugs protect vessels from damage. Besides, direct antioxidants decrease synthesis and increase catabolism of cholesterol and inhibit formation f thromboxane A_2. Thus, these drugs prevent destructive changes in vessels, their infiltration by lipids, fibrosis, and calcinosis.

Indirect antioxidants include such drugs as glutamic acid, methionine, cysteine, Preductal, sodium selenite, emoxypine, dibunol (butylated hydroxytoluene), etc. These drugs promote accumulation of glutathione which restore oxidized forms of tissue antioxidants and activity of peroxidases inactivating peroxides and hydroperoxides. Therapeutic effect of these drugs is mediated by their participation in phospholipid biosynthesis and hepatic oxidation of fatty acids.

Therapy with antioxidants is intended for 2–3 months in winter-spring period when intake of antioxidants with food is restricted.

Probucol (Lorelco) is synthetic antioxidant playing an importance role in therapy of atherosclerosis. The drug slows down lipid peroxidation, decreases uptake of LDL by cells of vascular

intima, and promote reduction of vascular accumulation of cholesterol. Probucol reduces plasma concentration of LDL. It should be noticed that the drug is effective in marked hereditary disorders of lipid metabolism, when statins are ineffective. Probucol is well tolerated by patients. The drug is taken orally in dose 0.5 g two times a day at mealtime. At II type hyperlipoproteinemia, therapeutic effect is observed in 1–3 months. Side effects of probucol are nausea, appetite loss, abdominal pain, and diarrhea. Cardiac arrhythmias due to disorders of impulse conduction is rare complication of probucol therapy. The drug is commonly combined with other hypolipidemic drugs.

Drugs Decreasing Blood Concentration of Triglycerides

Fibric Acid Derivatives

Fibric acid derivatives (fibrates) include such drugs as *clofibrate, bezafibrate, gemfibrozil,* and *fenofibrate*.

Clofibrate was approved in medicine more than 30 years ago. In a body, clofibrate is metabolized into parachlorophenol hydroxyisobutyric acid exerting antiatherosclerotic activity. Effect of clofibrate develops in 2–5 days after therapy intitiation and reachs maximum in several weeks or months.

Mechanism of action of fibric acid derivatives is associated with the increase of activity of lipoproteinlipase in capillaries. In result, catabolism of triglycerides and VLDL is increased. Blood level of triglycerides is reduced on 40–50 %. Simultaneously, blood level of antiatherogenic HDL is increased. Due to increased hepatic catabolism of VLDL, concentration of cholesterol and triglycerides in hepatocytes is increased that enchances cholesterol utilization for synthesis of bile acids and their release with bile. But this effect increases risk of formation of bile stones.

Clofibrate is rather toxic drug. Its side effects include dyspepsia, drowsiness, skin rash, leukopenia, cardiac arrhthymias, vascular disorders, muscular pain, reduced libido, rhabdomyolysis, muscular

weekness, hepatothoxicity, risk of cholelithiasis, alopecia, and cancerogenesis (tumors of large intestine and neck of bile blader).

To decrease side effects, new derivatives of fibric acid was synthesized and approved in practice: bezafibrate (II generation), fenofibrate, and gemfibrozil (III generation). These drugs exert same or higher antiatherosclerotic activity as clofibrate and longer duration of action (fenofibrate acts about 24 hours).

Fibrates are used to treat II and III types hyperlipidemias, especially in patients with excesive body weight and diabetes mellites. Also, these drugs are used in the treatment for IV and V types hyperlipidemias (more common prescribed for patients with risk of pancreatitis) and to decrease risk of ischemic heart disease. Fibrates exert low efficacy or are ineffective at hereditary hyperlipidemias.

It should be noted that if level of triglycerides is not decreased for 3 months of treatment, therapy with fibrates should be discontinued.

Drugs Decreasing Blood Concentration of Cholesterol (LDL) and Triglycerides (VLDL)

Preparations of Nicotinic Acid

Nicotinic acid and its derivatives are effective to treat all types of hyperlipidemias, because decrease blood concentration of VLDL, LDL, and IDL. Total amount of triglycerides in blood is decreased on 20–30 %. Many clinicians consider intake of nicotinic acid in combination with diet as most optimal mode of initial monotherapy of atherosclerosis.

Nicotinic acid inhibits lipolysis in fat tissue, decreases hepatic synthesis of VLDL, LDL, triglycerides, and cholesterol, and increases activity of lipoprotein lipase.

Long-lasting intake of nicotinic acid is accompanied by an increase of HDL concentration. Transport of cholesterol from tissues to a liver and its utilization for synthesis of bile acids are increased.

Nicotinic acid is effective to treat II–V types hyperlipidemias. To treat hyperlipidemias, doses of nicotinic acid are about 100 times more than those which are used in hypovitaminosis.

Nicotinic acid is readily absorbed from gastrointestinal tract, partly metabolized and excreted with urine. Its typical side effects are skin hyperemia, itching, skin rash, and hot feeling. These effects are due to release of prostanoids from walls of small vessels and may be prevented by low doses of aspirin (about 0.125–0.25 g). Besides, dyspepsia, hepatic dysfunction, gastric ulcer, hyperglycemia are possible complications of nicotinic acid therapy. Nicotinic acid slows down thrombocytes aggregation and activates fibrinolysis. *Acypimox (Olbetam)* is derivative of nicotinic acid which is better tolerated by patients. But this drug is used seldom.

Unsatureted fatty acids

Clinical use of unsaturated fatty acids is based on the observations upon human populations of high north which traditionally use fats of sea fish and animals. Among these populations, atherosclerosis, ischemic heart disease, and myocardial infarction are practically not observed. Unsaturated fatty acids are represented by oleic, linoleic, linolenic, and arachidonic acids. These acids are easily integrated in body metabolism as source of energy, as well as source for synthesis of membrane phospholipids and prostanoids. Preparations of unsaturated fatty acids (*Omacor, Natalben Supra, cod liver oil,* etc.) are used as dietary additives for patients with atherosclerosis and for its prevention. *Cod liver oil* and its preparations are used in the treatment for II and V types of hyperlipidemias. These drugs are contraindicated in IV type hypelipidemia.

Moristerol is drug of plant origin with high content of polyunsaturated fatty acids. Moristerol reduces plasma level of atherogenic lipoproteins, decreases platelets aggregation, consolidates structure of capillaries, increases cholesterol excretion with bile and decreases its intestinal absorption. The drug is taken in

capsules or in granules at mealtime. Moristerol is used in the treatment for all types of hyperlipidemias.

Lipostabil in capsules contains complex of unsaturated fatty acids and derivative of theophylline. Lipostabil for injections contains same components together with vitamins PP and B_6 and adenosine 5-monophosphate. The drug is used in the treatment for atherosclerosis and disorders of coronary, cerebral, and peripheral circulation. Lipostabil is taken orally 1–2 capsules 3 times a day or administered intravenously slowly 10–20 ml. Lipostabil is well tolerated by patients.

Essentiale is co-formulated drug containing essential phospholipids – diglycidyl ethers of choline-phosphoric acid and unsaturated fatty acids together with vitamins: pyridoxine, cyanocobalamin, nicotinamide, pantothenic acid, riboflavin, and tocopherol. The drug activates cholesterol catabolism by means of formation of its ethers with unsaturated fatty acids, improves stability of protein-lipid complexes, increases cholesterol acceptor and cholesterol-transporting properties of blood and hepatic function. Essentiale is used as antiatherosclerotic and hepatoprotective drug: to treat ischemic heart disease, hepatitis, hepatic dystrophy and cirrhosis, toxic liver damage, alcoholism, etc.

These drugs are not used for monotherapy of atherosclerosis because under the background of unsaturated fatty acids intake, body level of cholesterol and triglycerides is decreased insignificantly.

Anticoagulants

Heparin exerts moderate ability to decrease blood level of cholesterol and triglycerides due to activation of lipoprotein lipase. Thus, heparin decreases blood level of atherogenic lipoproteins. Besides, heparin increases negative charge of endothelial cells of vascular wall, that prevents lipoproteins absorption and their interaction with mucopolysaccharides of vascular intima.

Angioprotectors

Endotheliotropic drugs (vasoprotectors or angioprotectors) are used in the complex therapy of atherosclerosis. These drugs decrease vascular permeability.

Parmidine (pyridinol carbamate) is representative of such drugs. The drug exerts antibradykinin effect, decreases oedema, and reduces permeability of vascular wall. Besides, parmidine improves microcirculation, reduces thrombocytes aggregation, promotes restoration of elastic and muscular fibers in sytes of cholesterol accumulation, and inhibits blood coagulation. Parmidine is taken oraly for several months. The drug is well tolerated by patients. Its side effects are nausea and allergic reactions.

Etamsylate (Dicynone) inhibits hyaluronidase activity that reduces destruction of mucopolysaccharides of vascular wall. The drug increases stability of capillaries and normalizes their permeability. Besides, etamsylate decreases bleeding and increases number of thrombocytes.

Quercetin is preparation of vitamin P. The drug decreases vascular permeability and angiasthenia. Together with ascorbic acid, quercetin participates in redox processes and inhibits hyaluronidase.

DRUGS WHICH USED TO TREAT OBESITY

Obesity is widely spreaded metabolic disorder which is manifested by excessive accumulation of fat. The coses of obesity are low physical activity and excessive intake of calorigenic foods: animal fats, starchy and confectionery products, etc., and insufficient intake of proteins, plant oils, fresh vegetables and fruits. Aberrations of food regimen promotes obesity: dry food, fast food, and overnutrition at evening. Besides, there is genetic disposition to obesity. A risk of obesity increases with age, at psychical and endocrine disorders.

In turn, obesity is a risk factor of diabetes melites, atherosclerosis, hypertension, ischemic heart disease, arthritis, etc. At obesity, a lowering of body wheight is accompanied by decrease of

risk of myocardial infarction, cerebral stroke, and other complications which lead to disability and death.

Traditionally, treatment of obesity is based on diet and physical activity, surgical resection of fat tissue, body fat suction, and drug therapy.

Drugs which are used to treat obesity are classified as follows.

1. Drugs decreasing appetite (anorexigenic drugs).

1.1. Drugs influencing catecholaminergic system: *mazindol (Sanorex), chlorphentermine (Desopimon), amfepramone (Phepranon).*

1.2. Drugs influencing catecholaminergic and serotoninergic systems: *fenfluramine* and *sibutramine*.

2. Drugs stimulating lipolysis and thermogenesis (β_3-adrenergic agonists): *mirabegron.*

3. Drugs violating intestinal fats absorption: *orlistat.*

4. Drugs substituting fats: *olestra*.

5. Drugs substituting carbohydrates: *aspartame* and *saccharin*.

Besides mentioned drugs, phytotherapy with dietary additives is widely used to correct metabolism and to decrease appetite. Such dietary additives are reach by vitamins, minerals, polyunsaturated fatty acids, amino acids, and dietary fibers. These preparations promote elimination of cholesterol and other metabolic products from the body. An advisability of the dietary additives use is obvious, but their efficacy should not be overstated.

Drugs Decreasing Appetite

Drugs Influencing Catecholaminergic System

Phenamine was one of the first anorexigenic drugs. Phenamine exerts central and peripheral indirect adrenomimetic action. The drug increases release of norepinephrine and dopamine from adrenergic nervous terminals and inhibits their neuronal reuptake. Phenamine stimulates brain's satiation center that leads to reduction of hunger center activity. Besides, the drug is potent psychostimulant. Therefore, its use to treat obesity is accompanied by insomnia, tachycardia, hypertension, anxiety, etc. Also, phenamine can cause psychical and physical dependence.

In medicine, such drugs as *amfepramone (Phepranon)* and *chlorphentermine (Desopimon)* are used to treat obesity. These drugs exert same mechanism of action as phenamine. But anorexigenic effect of these drugs is less. Besides, these drugs stimulate central nervous system in less degree, and their peripheral side effects are less expressed. The drugs are taken orally in 30 minutes before a meal at first part of day. Their possible side effects are tachycarida, cardiac arrhythmias, hypertension, anxiety, insomnia, etc. Besides, these drugs can cause tolerance and drug dependence.

Mazindol (Sanorex) exhibits 5–10 times higher anorexigenic activity than phenamine. Its mechanism of action is similar to mechanism of action of phenamine. Besides, the drug inhibits intestinal absorption and body synthesis of triglycerides and decreases cholesterol level. The drug is taken orally at first part of day. Mazindol intake is accompanied by low risk of drug dependence. Its side effects are insomnia, dry mouth, dyspepsia, and allergic reactions.

Drugs Influencing Catecholaminergic and Serotoninergic Systems

Fenfluramine and *sibutramine* exert sedative influence upon central nervous system. Their mechanism of action is associated with stimulation of neuronal release of catecholamines and serotonin. Besides, these drugs inhibit neuronal reuptake of these mediators and increase metabolism of serotonin in the brain. The drugs inhibit intestinal absorption of lipids and body synthesis of triglycerides. Their possible side effects are hypertension, tachycardia, dyspepsia, insomnia, and depression.

During last years, anorexigens inhibiting cannabinoid (CB-1) receptors was approved in medicine. These group is represented by *rimonabant (Acomplia).* The drug is taken orally. Its anorexigenic efficacy is similar to efficacy of sibutramine. Rimonabant is well tolerated by patients. Its possible side effects are dyspepsia, depression, and dizinness.

Drugs Stimulating Lipolysis and Thermogenesis (β_3-Adrenergic Agonists)

It is known that stimulation of β_3-adrenergic receptors leads to activation of lipolysis and thermogenesis. This fact was a base for creation of new group of drugs to treat obesity. The therapy with β_3-adrenomimetic mirabegron is accompanied by decrease of body wheight in all patients; but this drug is not broadly used nowadays.

Drugs inhibiting intestinal absorption of fats

This group is represented by *orlistat (Xenical)*. The drug violates fat absorption due to inhibition of intestinal lipase. Violation of hydrolysis of triglycerides reduces their intestinal absorption and absorption of cholesterol about 30 %. Taken orally orlistat is excreted in unchanged form by intestine during 3–5 days. Its side effects are abdominal pain, diarrhea, nausea, vomiting, steatorrhea.

Drugs Substituting Fats

Different low-calorie or poorly absorbed substitutes of fats are used to treat obesity. Their tast is similar to tast of fats. *Olestra* is representative of these drugs. The drug consists of esters of sucrose with various long chain fatty acids. Olestra is not absorbed from gastrointestinal tract and reduces absorption of fat-soluble vitamins, cholesterol, and bile acids. The drug can cause abdominal pain and diarrhea.

Drugs Substituting Carbohydrates

Aspartame and saccharin are carbogydrate substitutors which used to reduce caloric content of food. Their tast is similar to tast of sugar, but these drugs are poorly absorbed from gastrointestinal tract and their calorific value is low.

Research of new drugs to treat obesity continue. Findings of leptin (hormone of fat tissue) and melanocortin show that these hormones are able to decrease appetite. A creation of corresponding drugs of these hormones allows to treat obesity with higher efficacy.

At the same time, it is finding that some peptides (neuropeptide Y, orexin) stimulate appetite. Nowadays, active search of their antagonists is in progress. Cholecystokinin, produced by cells of digestive system, stimulates satiety and creation of drugs on its base is also perspective.

DRUGS TO TREAT OSTEOPOROSIS

Osteoporosis is a group of metabolic diseases of bones which characterized by reduction of density of bone mineralization, due to that bones became porous and fine. A resistance of bones to mechanical influences reduced that leads to increased risk of bone fractures and is a common cause of disability and mortality. These problems are widely spread between young people and, especially, between people of moderate and old age.

It is known that bone tissue is permanently restored. Osteoclasts perform resorption of bone and osteoblasts are responsible for growth of bone tissue. Weight of bones reach maximum about 30 years old, after that it is gradually decreased. To 75 years old, bone mass is reduced on 30–50 %. Osteoporosis develops due to violation of dynamic equilibrium between bone resorption and their formation. These processes are regulated by estrogens, androgens, growth hormone, parathyroid hormone, corticosteroids, calcitonin, vitamin D and its metabolits, special proteins regulating activity of osteoclasts, cytokines, calcium ions, etc. Physical exercises and genetic factors play an important role in maintenance of bone mineralization.

Drugs which are used to treat osteoporosis are classified as follows.

1. Hormonal drugs and their analogues.

1.1. Sex hormones: *estrogens*, *androgens*, and *anabolic steroids.*

1.2. *Calcitonin.*

2. Active metabolites of vitamin D: *alfacalcidol* and *calcitriol.*

3. Combined drugs of animal origin: *ossein-hydroxyapatite.*

4. Synthetic drugs.

4.1. Bisphosphonates: *etidronate, pamidronate,* and *alendronate.*

4.2. Fluorides: *sodium monofluorophosphate* and *sodium fluoride.*

4.3. Calcium preparations: *calcium carbonate* and *calcium citrate.*

4.4. Strontium salts: *strontium ranelate.*

As a rule, osteoporosis is observed in old patient and is associated with reduction of sex hormones production. Especially, osteoporosis is common in women after 50–55 years and is associated with reduced amount of estrogens in menopause. In this case, *estrogens* are prescribed to prevent osteoporosis. A course of treatment lasts 5–10 years. Estrogens inhibit function of osteoclasts that decreases bone resorption. But such therapy increases the risk of breast and uterine cancer. Therefore, estrogens are combined with progestins to decrease risk of cancer.

Calcitonin is produced by thyroid gland. It reduces bone resorption by means of direct inhibition of osteoclasts activity. Besides, the hormone exerts analgesic activity owing to influence central nervous system. In medicine, a lot of different preparations of calcitonin is used: *synthetic human calcitonin, natural pork calcitonin, Miacalcic* (synthetic salmon's calcitonin), *Elcatonin* (eel's calcitonin), etc.

Chemical structure and activity of *Miacalcic* is similar to those of human calcitonin. Miacalcic is dosed in international units and administered subcutaneously, intramuscularly, and intranasaly (as spray). The drug regulates calcium metabolism, decreases increased blood concentration of calcium due to inhibition of bone resorption and inhibition of renal reabsorption of calcium. Miacalcic is used to treat menopausal, senile, and corticosteroid-induced osteoporosis. Especially, therapy with Miacalcic is reasonable at osteoporosis which is accompanied by pain. Side effects of Miacalcic include

dyspepsia, hyperemia of face, inflammation at the sites of drug administration.

Active metabolites of vitamin D (*calcitriol* and *alfacalcidol*) promote intestinal absorption of calcium and phsophates, increase calcium renal reabsorption, stimulate removal of calcium and phosphates from the bones in the blood. Owing to these effects, metabolites of vitamin D maintain necessary blood concentration of calcium and phosphates, that provides favorable conditions for bone mineralization.

Calcitriol is active metabolite of vitamin D, activity of which is increased under influence of parathyroid hormone. It is considered that calcitriol deficiency is a cause of osteoporosis and hyperparathyreosis at renal failure. Calcitriol is taken orally or administered intravenously. At oral intake, calcitriol acts during 3–5 days. The drug is metabolized in the liver and excreted with bile in the intestine. Effects of *alfacalcidol* are softer. The drug causes hypercalcemia seldom. Alfacalcidol is taken orally in capsules.

Overdose of active metabolites of vitamin D leads to increase of calcium concentration in blood, anorexia, vomiting, nausea, constipation, and stupor. In such cases, high doses of calcitonin, loop diuretics, and large amount of fluids are prescribed to patient. At acute overdose of calcitriol, gastric lavage is also recommended.

Ossein-hydroxyapatite (Osteogenon) is obtained from animal bones. It is supposed that the drug activates osteoblasts and inactivates osteoclasts; but its mechanism of action is unknown completely. Its side effects are observed seldom and include nausea, hypercalcemia, and allergic reactions. Osteogenon is used to treat osteoporosis in combination with other drugs.

Bisphosphonates (*etidronate, pamidronate, alendronate,* etc.) bind with crystals of hydroxyapatite of bones and are kept in bone tissue during several months or years. At bone resorption, bisphosphonates are locally released from the tissue and inhibit activity of osteoclasts that leads to a decrease of bone resorption.

Bisphosphonates are poorly absorbed from gastrointestinal tract (about 10 %). These drugs decrease blood concentration of calcium

and phosphates and may be used to eliminate hypercalcemia. Bisphosphonates are tolerated by patients well and used to treat and prevent osteoporosis by courses lasting from several months to a year and more. These drugs are classified in 3 generations. II-Generation (alendronate and pamidronate) and III-generation (risedronate and bondronat) drugs are preferable than I-generation drugs (e. g., etidronate) because these drugs do not inhibit bone calcification and do not cause osteomalacia. Bisphosphonates are used to treat osteoporosis, hypercalcemia, hyperparathyroidism, bone tumors, and Paget's disease. Their side effects are dyspepsia, myalgia, lymphocytopenia, hypocalcemia, etc.

There is no consensus about usefulness of fluorides in the treatment for osteoporosis. But some clinicians prescribe these drugs noting their positive effect. Fluorides stimulate osteoblasts and promote their proliferation. These drugs are taken orally; their bioavailability is about 100 %. Significant part of absorbed sodium fluoride enters bones, rest is excreted with urine. Course of treatment lasts 4–6 months. Fluorides have a narrow therapeutic window. Their intake is accompanied by dyspepsia, osteomalacia, etc.

There is evidence that teriparatide (active residue of human parathyroid hormone) stimulates osteoblasts and increases density of bone trabecules. For this aim, the small doses of drug are prescribed by intermittent courses. But these data need additional investigations.

To prevent osteoporosis, calcium preparations (carbonate, phosphate, lactate, etc.) are commonly used in combination with other minerals. Osteomag and Osteomag forte contain calcium carbonate, cholecalciferol, magnesium, copper, zinc, manganese, and boron. These drugs are taken orally. Preparations eliminate deficiency of micro- and macroelements in a body.

Anabolic steroids (Retabolil, Phenobolin, etc.) increase bone mass and decrease osteoporosis. But their use is restricted by sucg side effects as masculinization, increase of blood concentration of atherogenic lipoproteins, and dyspepsia.

Strontium ranelate stimulates grouth of bone tissue and inhibits its resorption. The drug is taken orally and readily absorbed from

gastrointestinal tract. Strontium ranelate is tolerated by patients well. Its side effects include headache and dyspepsia.

DRUGS TO TREAT DYSTROPHIC CHANGES OF CARTILAGINOUS TISSUE (OSTEOCHONDROSIS AND OSTEOARTHROSIS)

Diseases of cartilaginous tissue are quite spread. At least 1/3 peoples after 50 years are suffering from these diseases. But dystrophic changes of cartilaginous tissue continue to spread between under 50-years old humans.

Cartilaginous capping of joints and synovial fluid provide mobility of joints. Cartilaginous tissue has not vessels; therefore, its supporting by necessary compounds is provided due to diffusion of substances from bone's epiphysis. Disorders of blood circulation in epiphysis lead to dystrophic damage of cartilaginous tissue. This process is accompanied by inflammation, pain, and disorders of mobility in joints. As a rule, non-steroid anti-inflammatory drugs are used to treat acute inflammatory processes in joints. Glucocorticoids are prescribed in cases of severe inflammation. These drugs decrease pain and improve joint mobility, but their effects are temporal and need additional use of drugs stimulating regeneration and functions of cartilaginous tissue.

Rumalon is extract of cartilages and bone marrow of calves. The drug is administered intramuscularly. Commonly, Rumalon is called as chondroprotector. Rumalon stimulates synthesis of components of synovial fluid and extracellular matrix. Besides, Rumalon accelerates cartilages regeneration and inhibits activity of enzymes which decrease density of tissues. Rumalon is prescribed several times for year by courses lasting 20–25 days. The drug slows down progress of osteochondrosis and promotes regeneration of cartilageous tissue. Side effects of Rumalon are allergic reactions.

Structum is polysaccharide which participates in formation of ground substance of bone and cartilaginous tissue and slows down substitution of its cells by components of connective tissue. Structum

is taken orally in capsules. Course of treatment lasts 3 months and more. Side effects of Structum are allergic reactions.

Ascorbic acid and *tocopherol* are essential for regeneration of cartilaginous tissue. Ascorbic acid (vitamin C) provides includion of sulfur in mucopolysaccharides in process of formation of cartilaginous tissue and hyaluronic acid (main ground substance of connective tissue and synovia). Besides, vitamin C is essential for synthesis of hydroxyproline and collagen, participates in formation of cartilage skeleton and bone osein, and promotes wound healing. Also, antioxidative properties of ascorbic acid are important.

Tocopherol (vitamin E) is one of the most potent antioxidants. Therefore, it considered as one of the essential components in osteochondrosis treatment, because aggressive influence of free radicals plays an important role in pathogenesis of this disease. Tocopherol is prescribed orally or intramuscularly in high doses by long-lasting courses.

Also, vasodilators, irritative and anti-inflammatory drugs are used in osteochondrosis treatment. These drugs increase blood supply of joints that improves tissue trophicity.

DRUGS USED TO TREAT GOUT

Gout is a chronic disease which develops due to disorders of purine (adenine and guanine) metabolisim that leads to hyperuricemia and formation of microcristalls of sodium salt of uric acid in cartilages, stratum synoviale, joint oil, kidneys, and soft tissues.

There are primary (idiopatic) and secondary gout. Idiopathic gout is associated with gereditary abnormality of enzymes participating in purine metabolism: reduced activity of hypoxanthine-guanine phosphoribosyltransferase and adenine-phosphoribosyl pyrophosphate synthase leads to increase of uric acid synthesis.

Most commom causes of secondary gout are renal diseases with violation of their ability to excrete nitrous compaunds, polycitemia, chronic intoxication by lead, and leukemia in period of cytostatic

therapy (massive degradation of blood cells is accompanied by release of nuclear purine bases.

Consumption of alcohol, tea, coffee, and food with increased amount of purines (meat, fish, mushrooms, etc.) promotes gout development.

It is known that uric acid is final product of purine metabolism. In extracellular fluid, where sodium is a main cation, uric acid is transformed from ionized state to sodium salt. This salt is poorly soluble in water, therefore insignificant increase of its concentration in extracellular fluid leads to formation of crystals of sodium urate. Formation of such crystals in the hoints causes gout and acute inflammatory arthritis, in renal intesrsticium – gouty nephropathy and nephrolithiasis, in the soft tissues – formation of tophaceous gout.

Inflammation of joints is associated with uptake by neutrophils of sodium urate crystals. Crystals affect lysosomal membranes, cause destruction of cells, and, therefore, induce free-radical processes (superoxide radicals are formed) and release of bioactive substances (prostaglandin E_2, leukotriene B_4, interleukin-1, etc.) from damaged polymorphonuclear leukocytes and monocytes.

From a body, uric acid is excreted kidneys. It is filtered in glomeruli and reabsorbed practicly completely in proximal convoluted tubules. Distally in proximal tubules, uric acid is secreted secondary and andergoes repeated reabsorption. Normal, clearance of uric acid is about 10 % of volume of its filtrate.

Excretion of large amount of urates may lead to formation of crystals. This process is increased due to acidic reaction of urine and inflammatory processes in kidneys.

Drugs to treat gout are classified as follows.

1. Anti-inflammatory drugs (used to treat acute gout, do not influence hyperuricemia): *colchicine,* steroid anti-inflammatory drugs *(prednisolone, dexamethazone),* and nonsteroid anti-inflammatory drugs *(indomethacin, diclofenac sodium, phenylbutazone).*

2. Drugs decreasing blood concentration of uric acid.

2.1. Drugs reducing uric acid synthesis: *allopurinol* and *febuxostat*.

2.2. Drugs increasing uric acid excretion by kidneys (uricosuric drugs): *sulfinpyrazone, etabenecid, probenecid, urodanum, solimok*.

2.3. Drugs inhibiting synthesis and excretion of uric acid: *benzbromarone* and *Allomaron* (containing allopurinol and benzbromarone).

Drugs of 2.2 and 2.3 groups are used to prevent gout attacks.

Solimok, Uralyt-U, and *Blemaren* are used to treat nephrolithiasis with domination of stones of urates.

Allopurinol (Milurit) is the inhibitor of xanthine oxidase (enzyme which catalizes the transformation of hypoxanthine and xanthine into the uric acid). The drug suppresses the synthesis of uric acid, decreases blood concentration of uric acid and its excretion with urine. Excretion of hypoxanthine and xanthine with urine is increased, but water solubility of these substances is higher than solubility of uric acid. In a body, allopurinol is metabolized into alloxanthine which also exerts ability to inhibit xanthine oxidase activity, but in less degree than allopuriniol. Thus, allopurinol decreases synthesis of uric acid and xanthine and hypoxanthine become the main final products of purine metabolism.

Allopurinol is used to treat chronic gout, renal pathology or renal stones against background of hyperuricemia, tophaceous gout, and in patient showing significant and constant high plasma concentration of urates.

Acute gout attack may arise during initial period of treatment by allopurinol. To prevent such complication, the drug is prescribed in minimal doses for first days of treatment. It is necessary to maintain diuresis on level at least two litres per day; pH of urine should be neutral or weakly-basic. Allopurinol is not used at gout attacks and during 3–4 week after it. Besides, it is reasonable to combine allopurinol with colchicine which is able prevent gout exacerbation. Allopurinol can cause such side effects as nausea, vomiting, diarrhea, peripheral neuritis, necrotizing vasculitis, inhibition of hemopoiesis

(even aplastic anemia), hepatic and renal damages, allergic reactions, etc. Allopurinol is deposited in lens with following development of cataract. The drug is contraindicated in pregnancy, lactation, to persons suffering from idiopathic hemochromatosis, etc.

Febuxostat (Adenuric) is new selective inhibitor of xanthine oxidase which decreases uric acid level in plasma of patients with chronic gout and violated renal function. In comparison with allopurinol, febuxostat has some advantages. Its therapeutic action is associated with reduction of blood concentration of uric acid by means of marked inhibition of different form of xanthine oxidase which are able transform one to another due to exchange of molybdenum ions. Febuxostat inhibits enzyme due to simultaneous binding by strong bonds with both oxidated and reduced forms of xanthine oxidase. Allopurinol binds mainly with reduced form of xanthine oxidase by weak bond. It should be noticed that structure of allopurinol allows it to participate in purine reactions that reduces its therapeutic effect. Molecules of febuxostat block permeability of narrow molybdenum channels that leads to stable inhibition of xanthine oxidase activity. Even first taken dose of febuxostat leads to long-lasting inhibition of enzyme. Therefore, therapeutic effect of the drug develops due to intake of less doses and less blood concentration of febuxostat.

Unlike allopurinol, therapeutic doses of febuxostat do not affect other enzymes participating in purine and pyrimidine metabolism (guanine deaminase, orotidine 5'-phosphate decarboxylase, and purine nucleoside phosphorylase).

Febuxostat is rapidly absorbed after oral intake. Its degree of binding with plasma proteins is about 100 %. The drug is metabolized only in liver by means of cytochrome P-450 system and conjugation by UDP-glucuronosyltransferase. Its half-life is 5–8 hours. Renal excretion of febuxostat and its metabolites is less than 10 %; therefore, the drug is used in the treatment for gout in patients with chronic renal failure. It should be noticed that allopurinol, renal excretion of which is about 80 %, is contraindicated at chronic renal failure.

In initial period of therapy, febuxostat can increase plasma concentration of uric acid, thereby initiation of therapy with this drug should not congruent with period of gout exacerbation. Therapy is initiated in the absence of exacerbation with simultaneous intake of non-specific anti-inflammatory drugs or colchicine. Febuxostat may be combined with indomethacin or naproxen because it does not influence pharmacokinetics of these drugs.

Considering that febuxostat inhibits xanthine oxidase, its use with azathioprine and mercaptopurine is not recommended, because such combination can lead to elevation of blood concentration of these drugs. Azathioprine and mercaptopurine are structural analogues (antimetabolites) of adenine, guanine, and hypoxanthine; these drugs are metabolized in a liver by means of xanthine oxidase with formation of 6-thiourea. The same may be said about febuxostat use together with theophylline, caffeine, and other drugs which metabolized with formation of uric acid as final product.

Besides, febuxostat is not recommended at secondary hyperuricemia arising due to cancer chemotherapy.

Sulfinpyrazone (Anturan) is pyrazolone derivative. The drug exerts uricosuric and antiagregative effects. Sulfinpyrazone increase renal excretion of uric acid owing to reduction of its reabsorption in proximal convoluted tubules. Besides, the drug decreases renal excretion of benzylpenicillin. After several weeks of treatment, Anturan promotes significant reduction of intensity and frequency of gout attacks, decreases joint pain and improves their mobility. Later, elimination of tophus and periartricular depositions of uric acid are observed. Also, the drug prevents formation of new lesions of gout. Therapy with sulfinpyrazone should be started at least in 2–3 weeks after the end of acute gout attack.

It should be noticed that sulfinpyrazone decreases adhesion and aggregation of thrombocytes, inhibits synthesis of thromboxane A_2, and protects vascular endothelium. In this regard, the drug may be used as alternative of acetylsalicylic acid. Because sulfinpyrazone irritates gastrointestinal tract it is taken at mealtime.

Side effects of sulfinpyrazone are gout exacerbation for firsts days of treatment, gastrointestinal disorders (even bleeding), skin rashes, and blood dyscrasias (aplastic anemia, leukopenia, thrombocytopenia, granulocytopenia, etc.). The drug intake should be discontinued if thrombocytopenia, leukopenia, or allergic reactions occurred. Sulfinpyrazone is contraindicated during exacerbation of erosive-ulcer lesions of gastrointestinal tract, functional disorders of liver and kidneys, etc.

Etabenecid (Aethamidum) and *probenecid* are derivatives of benzoic acid. Their mechanism of action is same with those of sulfinpyrazone. These drugs inhibit the reabsorbtion of uric acid in proximal convoluted tubules. Besides, both drugs decrease renal secretion of benzylpenicillin.

Etebenecid is used to treat chronic gout, polyarthritis with disorders of purine metabolism, nephrolithiasis and urolithiasis of urate origin.

Probenecid is used to treat symptomatic hyperuricemia and gouty arthritis in patients for which other drugs to treat hyperuricemia are contraindicated. Under probenecid action, an increase of uric acid excretion leads to elevation of its release from tissue depositions into blood that, in turn, can cause acute gout attack. Probenecid is contraindicated in acute gout attack and urolithiasis (especially at presence of urate concrements). Probenecid is no used in secondary hyperuricemia associated with cancer or therapy by chemotherapeutic drugs because this drug only increases secretion of uric acid and does not decrease its synthesis. Hyperuricemia, arising in this case, increases risk of nephropathy. The drug should be taken carefully by patients having ulcer disease in anamnesis. Probenecid may be ineffective in patients with chronic renal failure, especially if level of glomerular filtration is less than 30 ml / min.

Urodanum is co-formulation containing piperazine phosphate, hexamethylentetramine, lithium benzoate, and some other salts which increase urine pH. Besides, lithium salts and piperazine form easily soluble salts with uric acid that increases its excretion from

a body. The drug is used to treat gout, nephrolithiasis, spondyloarthritis, and chronic polyarthritis.

Benzbromarone (Hipurik, Minurik) exerts hypouricemic and uricosuric effects. Hypouricemic effect is associated with inhibition of enzymes participating in purine synthesis, and uricosuric action is due to inhibition of uric acid reabsorption in proximal convoluted tubules and increased its excretion by kidneys. The main indications for use of benzbromarone are gout, hyperuricemia, psoriasis, and hematological diseases.

Allomaron is co-formulated drug containing allopurinol and benzbromarone. The drug exerts hypouricemic and uricosuric effects.

Colchicine is alkaloid obtained from *Colchicum autumnale*. The drug exerts marked anti-inflammatory effect at acute gout attacks. Colchicine inhibits proliferation of granulocytes and their migration into inflammatory regions. Besides, colchicine reduces phagocytosis of crystals of uric acid salts and slows down their deposition in tissues. The drug prevents mytosis and degranulation of neutrophils, stabilizes lysosomal membranes, decreases release of lysosomal enzymes, and inhibits synthesis of prostaglandins and leukotriene B_4 which are mediators of acute gouty inflammation. Also, colchicine decreases formation of lactic acid and prevents tissue acidosis and, due to this, restricts crystallization of urates. It must be understood that between these mechanisms there are no reduction of uric acid concentration in blood and elevation of its body excretion.

Colchicine is readily absorbed in gastrointestinal tract. Its maximum concentration in plasma is observed about 1–2 hours after oral intake. the drug is excreted from a body by kidneys and intestine.

Anti-gout efficacy of colchicine is reduced by cytostatics and drugs which acidifying urine. And vice versa, drugs, enhancing pH of urine, increase colchicine efficacy.

Colchicine is used to treat gout, to facilitate patient state at acute gout, and to prevent gout exacerbation (especially during first several

months of therapy with allopurinol and drugs promoting uric acid excretion).

Blemaren allows maintain urine pH within interval 6,6–6,8 that creates optimal conditions to increase dissolution of uric acid salts.

Long-lasting intake of blemaren leads to dissolution of urate stones and prevents their formation. Blemaren is used to treat urolithiasis with domination of urates and to prevent formation of urate stones.

Solimok is co-formulation containing potassium citrate, sodium citrate, and citric acid. The drug increases urine pH and promotes dissolution of urate stones, decrease of their size, and their spontaneous discharge. Solimok is used to treat gout, and in cases of occurrence of urate stones in kidneys, ureters, or bladder.

Like Solimok, *Uralyt-U* contains potassium citrate, sodium citrate, and citric acid. The drug maintains urine pH within range 6,2–7,5 when uric acid salts are soluble and do not form concrements. The drug is used to dissolve urate concrements and to prevent their following formation. Besides, Uralyt-U is used during ttherapy with cytostatics and in the treatment for porphyria cutanea tarda.

Tablte 14 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Aethamidum	Orally 0.35 g 4 times a day	Tablets 0.35 g
Allopurinolum	Orally 0.1–0.2 g once a day	Tablets 0.1 g
Febuxostatum	Orally 0.08–0.12 g 1 time a day	Coated tablets 0.08 or 0.12 g

Step 1. Tasks for Self-Control
Drugs to Treat Goat

1. A 42-year-old man suffering from gout has increased level of urinary acid in the blood. Allopurinol was prescribed to decrease the level of urinary acid. Competitive inhibitor of what enzyme is allopurinol?

A. Adenine phosphoribosyltransferase.
B. Xanthine oxidase.
C. Guanine deaminase.
D. Adenosine deaminase.
E. Hypoxantine phosphoribosyltransferase.

2. A doctor administered allopurinol to a 26-year-old man with symptoms of gout. What pharmacological action of allopurinol ensures therapeutic effect?

A. General analgesic effect.
B. General anti-inflammatory effect.
C. Inhibiting leucocyte migration into the joint.
D. Increasing uric acid excretion.
E. Inhibiting uric acid synthesis.

3. Acute uric acid nephropathy, which is characterized by the acute overproduction of uric acid and by extreme hyperuricemia, can best be prevented with which of the following?

A. Sodium chloride.
B. Aethamidum.
C. Allopurinol.
D. Amiloride.
E. Antidiuretic hormone.

4. The most widely used agent for the treatment of acute gouty arthritis is:

A. Phenylbutazone.
B. Allopurinol.
C. Probenecid.
D. Colchicine.
E. Indomethacin.

5. The mechanism by which probenecid lowers plasma levels of uric acid is by:

A. Promoting tubular reabsorption of uric acid.
B. Inhibiting production of uric acid in the liver.
C. Promoting tubular secretion of uric acid.
D. Inhibiting breakdown of purines to uric acid.
E. Inhibiting proximal tubular reabsorption of uric acid.

6. Allopurinol reduces serum urate levels by:

A. Promoting tubular reabsorption of uric acid.
B. Inhibiting uric acid synthesis.
C. Impairing renal urate reabsorption.
D. Decreasing metabolism of uric acid.
E. Promoting the active secretion of uric acid in kidneys.

PLASMA SUBSTITUTES SOLUTIONS FOR MAINTAIN OF WATER-SALT AND ACID-BASIC BALANCE DRUGS FOR PARENTERAL NUTRITION

Plasma Substitutes

Plasma substitutes are drugs which are used to restore normal circulating blood volume. These drugs should have sufficient molecular weight to prevent penetration of drug molecules from bloodstream into tissues and to maintain stable osmotic pressure. Plasma substitutes should be nontoxic and easily excreted from a body.

Donor blood *plasma* contains all components of the fluid part of human blood. Fresh frozen plasma is stored up to 6 months; dried plasma is kept during several years. Plasma is used to eliminate circulating blood volume deficit in severe bleeding, plasma loss, or dehydration, to improve rheological blood properties, and to decrease the risk of thrombosis.

Hypotonic, hypertonic, and isotonic blood plasma are used. Plasma is administered intravenously drop-by-drop or as intravenous

push. Administered plasma should be identical with the blood group of the recipient. Volume of administered plasma is 0.5–2 *l*. Plasma administration may provoke allergic reactions.

Ceruloplasmin freeze-dried for injections is a copper-containing glycoprotein relating to α-globulin fraction of the blood serum. The drug stabilizes cellular membranes, normalizes lipid peroxidation, stimulates erythropoiesis, exerts detoxifying action, etc. Therapeutic indications for ceruloplasmin are blood loss, intoxication, anemia, sepsis, oncological diseases, etc.

Dextrans are polysaccharides dissolved in isotonic solution of sodium chloride or glucose. Dextrans are obtained from culture of some microorganisms. Dextran preparations are *polyglucin* (molecular weight about 60 000) and *rheopolyglucin* (molecular weight about 35 000). Due to less molecular weight, rheopolyglucin influences rheological properties of the blood positively and reduces platelet aggregation. Rheopolyglucin is used to treat ischemic stroke, myocardial infarction, acute pancreatitis, significant blood loss, etc. The drug is administered in postoperative period to decrease thrombosis risk. Administered volume varies from 400–1 200 ml up to 2 500 ml. In a body, dextrans undergo partial hydrolysis and are excreted by kidneys. Dextrans are contraindicated in craniocerebral injury with increased intracranial pressure and in hemorrhagic stroke.

Rheogluman is co-formulation containing 10 % dextran solution, 5 % mannitol solution, and isotonic sodium chloride solution. Its properties are similar to the properties of rheopolyglucin. Besides, the drug stimulates diuresis.

Gelatinol is a hydrolyzate of gelatin with molecular weight 20 000. The drug increases circulating blood volume, decreases platelet aggregation, and eliminates metabolic acidosis. Therapeutic indications for gelatinol are blood loss, intoxications, acute pancreatitis, hepatatis, peritonitis, etc. Gelatinol is administered as intravenous push or drop-by-drop.

Hemodez (*polyvidone*) is a solution of low-molecular-weight polyvinylpyrrolidone (molecular weight about 15 000) dissolved in

polyelectrolyte solution which contains cations of sodium, calcium, magnesium, and potassium, chlorine anions, and bicarbonate. Hemodez increases circulating blood volume, improves rheological properties of blood, collects interstitial fluid into bloodstream, and stimulates diuresis. Hemodez sorbs different toxins circulating in blood and eliminates them through the kidneys. Hemodez is used in the treatment for burn disease, severe dysentery, enterocolitis, sepsis, peritonitis, post-traumatic and postoperative intoxications, craniocerebral injuries with brain oedema, etc. About 80 % administered Hemodez is excreted from a body for 4 hours. Side effects of the drug are hypotension, tachycardia, and difficulty breathing. Contraindications for Hemodez are bronchial asthma, acute nephritis, and cerebral hemorrhage.

Neohemodez is a 6 % solution of low-molecular-weight polyvinylpyrrolidone with molecular weight 6 000–10 000 D. It is a complexing agent which binds toxins and excretes them with urine. The drug improves microcirculation and tissue oxygenation. Neohemodez improves renal circulation and stimulates diuresis. Neohemodez is administered intravenously drop-by-drop in the treatment for different intoxications. Its side effects are hypotension and allergic reactions.

Polydez is 3 % solution of low-molecular wheight polyvinyl alcohol in isotonic sodium chloride solution. The drug increases circulating blood volume, improves tissue oxygenation, exerts desintoxicated effect. Polydez is used in the treatment for blood loss, surgical shock, intoxications, sepsis, etc. The drug is administered intravenously drop-by-drop.

There are hypertonic and isotonic solutions of starch: *Refortan, Stabisol, HAES-steril,* and *Infukoll HES*. These drugs increase circulating blood volume, improve rheological properties of blood and microcirculation. The drugs are used in the treatment for sepsis and shocks.

Sorbitol is the hexatomic alcohol which is administered intravenously streamly or drop-by-drop. Sorbitol undergoes biotransfor-mation in liver with further formation of fructose which

provides dietery energy. Simultaneously, the concentrations of choline and glycogen are increased in a body. Therapeutic indications for sorbitol are blood loss, intoxications, hepatic diseases, renal failure, increased intracranial pressure, brain oedema, and pulmonary oedema.

Different solutions of electrolytes are used for intravenous administration to eliminate dehydration. Dehydration can result from vomiting or diarrhea, after surgery, in burns, severe blood loss, etc. Electrolyte solutions improve rheological properties of blood and restore circulating blood volume. The following electrolyte solutions are used in medicine: *isotonic sodium chloride solution, Ringer solution, Locke-Ringer solution, "Acesol", "Lactosol", polarizing mixture* (contains potassium chloride, glucose, and insulin), etc. If parenteral administration is impossible and contraindications are absence (unconsciousness, vomiting, penetrating wounds of abdomen, etc.), peroral administration of 1–1.5 *l* of electrolyte solution is used.

General contraindications for administration of electrolyte solutions are heart failure, risk of brain or lung oedema, cerebral hemorrhage, and acute renal failure.

Solutions without potassium are contraindicated in hyponatremia and hypokalemia; potassium-containing solutions are contraindicated in hyperkalemia and renal failure. Presence of bicarbonate or lactate sodium in some solutions (e. g., "Lactosol") allows to decrease severe damages and intoxications but do not eliminate disorders of acid-base balance.

Asparcamum (Panangin) is used to correct deficiency of potassium ions in a heart and intestinal wall. Asparcam is used to treat tachyarrhythmias (in myocardial infarction, overdose of cardiac glycosides), postoperative paresis of intestine, and paralytic ileus. Polarizing mixture is also used with same end in view.

Disorders of acid-base balance requires intensive therapy. Metabolic acidosis is the most common disturbance. Normal blood pH is 7.34–7.4. A decrease of pH to 7.3–7.25 is accompanied by metabolic and functional disorders. The following pathological

processes are developed in a body: multiple microthrombosis, hypoxia, increased vascular permeability, disorders of energy metabolism, and functional disorders of central nervous system, heart, kidneys, liver, and lungs. Compatible with life values of pH vary between 6,8–7,8. Buffered solutions, binding hydrogen ions and eliminating them through kidneys, are used to compensate acidosis. Preparations of buffered solutions are *trisamine, tromethamol, sodium hydrocarbonate, sodium lactate,* etc. These drugs are administered intravenously drop-by-drop.

Treatment of metabolic alkalosis is a significantly more difficult task. Alkalosis results in hypokalemia with disorders of heart rhythm and myocardial contractility, convulsions, disorders of neuromuscular transmission. *Ammonium chloride solution* and *diacarb* (*acetazolamide*) are used to correct alkalosis. In severe alkalosis, careful administration of *hydrochloric acid* in 5 % glucose solution is used under control of blood pH.

Drugs for parenteral nutrition are solutions of carbohydrates, lipids, and amino acids. These drugs are used when enteral nutrition is impossible: intestinal obstruction, severe diarrhea or vomiting, disorders of digestion and absorption, etc.

Isotonic (5 %) and hypertonic (10–40 %) *solutions of glucose* are administered intravenously. Isotonic glucose solution is used as plasma substituting agent to restore blood volume. Simultaneously, glucose is a nutrient. Hypertonic glucose solutions are administered to treat brain or pulmonary oedema. Administration of hypertonic solutions improves the detoxifying function of a liver and increases myocardial contractility and diuresis. Glucose solutions are used in the treatment for hypoglycemia, liver dystrophy, brain and lung oedema, cardiac decompensation, shock, and collapse. Glucose solution with methylene blue is used to treat poisoning by hydrocyanic acid.

Fat emulsions (*lipofundin, intralipid,* etc.) are used for intravenous administration. They are 10 % and 20 % emulsions of purified soybean and cottonseed oils, in which soybean phospholipids or egg yolk are used as an emulsifier. Energy value of

1 *l* of 20 % lipofundin is within the daily needs of a healthy person (about 2 000 kcal). Besides, fat emulsions provide the need of essential unsaturated fatty acids.

Amino acid solutions (*vamin, intrafusin, aminosol, aminosteril N-Hepa, hydrolysin, aminosol, aminoped*, etc.) are also used for parenteral nutrition. About 1–2 *l* of such solutions are administered in a body for providing daily amino acid requirements. Amino acid solutions are contraindicated in shock, acute hemodynamic disturbances, acute renal and hepatic failure, uremia, acidosis, and hypokalemia.

Acids and Alkalis. Salts of Alkali and Alkaline Earth Metals

Acids

Acids are required for maintenance of acid-base balance. Also, acids exhibit antimicrobial, local, reflex, and resorptive effects.

Antimicrobial effect of the acids is the result of the influence of hydrogen ion upon proteins of bacterial cells with the following their dehydration and denaturation.

Local effect of the acids occurs due to formation of albumins. Depending on concentration of hydrogen ions, the acid interacts with albumins that results in astringent, irritating, or cauterizing effects. Weak acids (most of organic acids) and strong acids (inorganic acids) in low concentrations exert astringent effect due to protein denaturation in superficial layers of skin and mucous membranes. Denaturation of proteins in deeper layers results in cauterizing effect.

Resorptive action of acids occurs due to interaction of hydrogen ions with buffer system of blood. It results in compensated and uncompensated acidosis.

Boric, salicylic, and *benzoic acids* are used topically. Boric acid exhibits astringent, anti-inflammatory, and antimicrobial (including antifungal) effects. In case of resorptive action, boric acid is accumulated in a body that leads to damages of kidney parenchyma.

Salicylic acid exerts keratoplastic (1–2 % solutions) and keratolytic (3–10 % solutions) effects. Besides, salicylic acid exhibits irritative, anti-inflammatory, antibacterial, and antifungal effects.

Benzoic acid is used as an antibacterial agent. In case of oral intake, benzoic acid stimulates bronchial secretion and may be used as an expectorant agent.

Diluted hydrochloric acid (3–8 % solutions) is taken orally to treat hypoacidic gastritis, dyspepsia, and hypochromic anemia. Also, hydrochloric acid exerts antimicrobial effect.

Poisoning by acids is accompanied by acidosis and symptoms of their influence upon mucous membranes (burns of gastrointestinal mucosa, gastric pain, vomiting, diarrhea, and painful shock). Uncompensated acidosis can cause loss of consciousness, dyspnea, sudden increase in blood pressure, and convulsions. Death develops due to respiratory paralysis. Treatment of poisoning includes the following measures: neutralisation of acids, gastric lavage with water or suspension of magnesium oxide, and intake of covering agents (e. g., milk, egg white). To prevent shock, opioid analgesics (e. g., morphine, promedol) are administered. To reduce acidosis, sodium hydrocarbonate is administered orally, rectally, or intravenously. Simptomatic therapy is also used.

The following amino acids which are used in medicine *glutamic acid, methionine, glycine, cysteine, histidine, taurine*, etc. Glutamic acid is used in the treatment for central nervous system diseases: epilepsy and psychosis. Methionine is used to treat liver diseases and dystrophy. Therapeutic indications for histidine are hepatitis and ulcer disease of stomach or duodenum. Glycine is used in the treatment for depression and alcoholism. Cysteine and taurine are used in ophthalmology.

Alkalis

Sodium hydrocarbonate is used as cleansing agent in the treatment for inflammatory diseases of mucosa. The drug exerts antibacterial, antimicotic, and irritative effects. Also, sodium hydrocarbonate improves microcirculation. In case of oral intake,

sodium hydrocarbonate exhibits antacid and expectorant effects. Solution of sodium hydrocarbonate is administered intravenously to reduce acidosis.

Magnesium oxide is an antacid with laxative effect.

Suspension of *aluminium hydroxide* is taken orally as an antacid and covering agent for treatment of hyperacidic gastritis and ulcer disease.

Ammonium solution is used as an antiseptic. Besides, this agent irritates the mucosa and reflexively stimulates respiratory centre. Therefore, it is used as a respiratory stimulant.

Drugs of Alkali and Alkaline Earth Metals

The main function of these drugs is to maintain ionic composition and osmotic pressure in the organism.

Sodium chloride. In medicine, sodium chloride is used in solutions of the following concentrations: isotonic (about 0.9 %), hypotonic (0.45–0.6 %), and hypertonic (2–10 %).

Isotonic sodium chloride solution is used for restoration of blood volume in collaps, shock, hemorrhage, diarhea, or vomiting. It is used for washing eyes and mucosa.

Hypertonic solutions are used for treatment of purulent wounds, for constipation, and for gastric lavage in poisoning with silver compounds.

Hypotonic solutions are used for preparation of local anaesthetic solutions (hypotonic solution prevents the absorption of the anaesthetic into the blood). Besides, 0.45 % solution is administered intravenously for treatment of hyperosmolar diabetic coma.

Potassium-contaning drugs are: *potassium chloride, Asparcamum, Panangin,* and *polarizing mixture*. These drugs are used for treatment of hypokalemia, tachyarrhythmias, ischaemic heart disease, and hypotrophy.

Calcium-containing drugs are: *calcium chloride, calcium gluconate, calcium glycerophosphate,* and *calcium lactate*. These drugs exhibit antiallergic and anti-inflammatory effects. The agents reduce the permeability of vessel walls. Calcium-

containing drugs are used for treatment of allergic diseases, bleeding, hypofunction of parathyroid glands, poisoning with magnesium salts and oxalic acid, osteoporosis, bone fractures, rickets, etc.

Magnesium-contaning drugs are *magnesium oxide* and *magnesium sulfate*. Magnesium sulfate exhibits the antispasmodic, anticonvulsive, sedative, curare-like, and ganglion blocking effects. In case of parenteral administration, magnesium sulfate lowers blood pressure and exhibits antiarrhythmic effect. Therapeutic indications for magnesium sulfate are hypertensive crisis, convulsions, eclampsia, tachyarrhythmias due to cardiac glycoside poisoning and hypokalemia.

Magnesium oxide is used as an antacid in the treatment for ulcer disease and hyperacid gastritis.

ANTIMICROBIAL AND ANTIPARASITIC DRUGS

ANTISEPTICS AND DISINFECTANT DRUGS

According to statistics, about 40–50 % of all human diseases are caused by different parasites (bacteria, spirochetes, rickettsia, chlamydia, fungi, viruses, and protozoa which account about 1 000 species). Besides, diseases may be caused by helminths and arthropods. Drugs, which are used to combat human pathogens, are divided into 2 groups:

– antiseptics and disinfectant drugs;

– chemotherapeutic drugs.

Antiseptics are used to combat human pathogens on the body surface (skin and mucosa). Sometimes, antiseptics are used to combat human pathogens in gastrointestinal and urinary tracts.

Disinfectant drugs are used to destruct pathogens in the environment: disinfection of medical instruments, medical supplies for nurses, dishes, clothes, rooms, and patient care equipment.

Antiseptics and disinfectants should have marked antibacterial and antiparasital effect. Simultaneously, these agents should be safe for human, don't irritate tissues, and don't damage instruments.

Division of drugs into antiseptics and disinfectants is somewhat relative, because some antiseptics in high concentrations are used for disinfection of the environment.

Chemotherapeutic agents are used to combat human pathogens into the organism. These drugs have high selective action upon certain species of microorganisms. Chemotherapeutic drugs should not affect the main functions of human organism. These drugs are used to prevent and treat infections.

It should be noted that some chemotherapeutic drugs may be used as antiseptics (e. g., furacilinum).

According to chemical structure, antiseptics and disinfectants are classified into the following groups:

1. Detergents: *cerigelum, aethonium, chlorhexidine, benzalconium chloride,* etc.

2. Nitrofuran derivatives: *furacilinum (nitrofural).*

3. Phenol group: *phenol, resorcin, ichthyol, wood-tar,* and *lysol*.

4. Stains: *brilliant green, ethacridine lactate (Rivanol),* and *methylene blue.*

5. Halogens:

– chlorine compounds: *bleaching powder, chloramine B,* and *pantocide*;

– iodine compounds: *alcohol solution of iodine, Lugol's solution, iodinol,* and *iodovidonum*.

6. Oxidisers: *hydrogen peroxide* and *potassium permanganate*.

7. Heavy metal compounds:

– silver-containing drugs: *silver nitrate, Protargolum,* and *Collargolum*;

– zinc-containing drugs: *zinc sulfate* and zinc *oxide*;

– copper-containing drugs: *copper sulfate*;

– mercury-containing drugs: *yellow mercury oxide, mercuric chloride (mercury (II) chloride),* and *mercury ammonium chloride*;

– bismuth-containing drugs: *bismuth nitrate, xeroform,* and *dermatol*.

8. Alcohols: *ethanol*.

9. Aldehydes: *formaldehyde* and *hexamethylenetetramine (urotropine).*

10. Acids and alkalies: *boric acid, salicylic acid, aqueous ammonium solution,* and *sodium hydrocarbonate solution*.

Detergents

Detergents are synthetic compounds with high surface activity which exhibit the marked antiseptic and detergent (washing) properties. Detergent drugs include organic substances containing two positively charged nitrogen atoms (cationic detergents) and some negatively charged compounds (anionic detergents). Detergent molecules are accumulated on the surface of the phase separation.

Antibacterial activity of detergents is due to their ability to decrease the surface tension that leads to disruption of cell membrane permeability of microorganisms. The ensuing disturbances of osmotic balance lead to death of microorganisms.

Anionic detergents include such agents as *green soap* and *laundry soap*. These agents are sodium or potassium salts of fatty acids with long hydrocarbon chain. Anionic detergents are less active than cationic detergents. Anionic detergents are used for laundry, wet cleaning, handwashing, disinfection, etc. Green soap is a component of Wilkinson's ointment.

Cationic detergents exhibit bactericidal effect against bacteria, fungi, viruses, and some protozoa. Cationic detergents include such agents as *cerigelum, miramistin, chlorhexidine*, etc. These agents are used for surgical hand preparation; disinfection of operative field and instruments; washing bladder, wounds, infected cavities, etc. Cationic detergents cannot be combined with anionic ones, because the antimicrobial activity reduces due to such combination. It should be noted that activity of cationic detergents is decreased in protein environment (e. g., presence of pus).

Nitrofuran Derivatives

Nitrofuran derivatives exhibit high antimicrobial activity and low toxicity. Thereby, these agents are used as both antiseptics and chemotherapeutic drugs. Drugs exhibit bacteriostatic or bactericidal effects depending on the doses used. Mechanism of nitrofuran's action is based on ability of their nitro groups to reduce into amino groups. Nitrofurans compete with natural hydrogen acceptors of microbial cells. Due to this ability, the agents slow down the cellular respiration and destroy energetic balance of microorganisms. Spectrum of antimicrobial action of nitrofurans includes Gram-positive and Gram-negative bacteria, fungi, and protozoa (chlamydia, giardia, and trichomonas).

Furacilinum (nitrofural) and *furazolidone* are derivatives of nitrofuran used as antiseptics. Water solution of furacilinum is used to treat wounds, burns, otitis; for nasal and pleural lavage. Eye

drops with furacilinum are used to treat conjunctivitis and blepharitis. Sometimes, furacilinum is used in dysentery treatment. Furacilinum is a component of such drugs as *Furaplastum* and *Lifusolum*. Furaplastum is used to treat wounds and minor skin injuries (bruises, scratches, cracks, etc.). The agent forms protective layer on the damaged surface and improves healing. Lifusolum, the drug aerosol, is used to treat wounds.

Antibacterial activity of *furazolidone* against gram-negative bacteria, giardia, and trichomonas is significantly higher than activity of furacilinum. Furazolidone is used mainly as chemotherapeutic agent.

Side effects of nitrofurans are dyspepsia, headache, disiness, and allergic reactions.

Phenol Group

Phenol is the oldest antiseptic agent. It is used as a standard to estimate activity of other antiseptics and disinfectants. Phenol in low concentrations exhibits bacteriostatic effect. Phenol in high (1–5 %) concentrations has bactericidal effect. Phenol destroys the permeability of the cell membrane and blocks the activity of dehydrogenase. The agent has a wide spectrum of action. Proteins do not reduce the activity of phenol.

Phenol easily penetrates through skin and mucous membranes. Poisoning by phenol is manifested by dizziness, weakness, dyspnea, tachycardia, sweating, and sonitus. Collapse and significant disturbances of respiration develop in severe cases. If phenol was taken perorally, a poisoned patient needs gastric lavage with vegetable oil. Affected regions of skin should be washed by 50 % ethyl alcohol or vegetable oil. In case of central nervous system depression, stimulating agents should be administered.

Phenol in form of 2–5 % carbolic soap mixture is used to disinfect rooms, supplies for nurses, clothes, and places contaminated with feces. With the same end in view, lysol and tricresol are used in medicine.

Vagothyl is a 36 % water solution of polyethylene-metacresol-sulfonic acid. The drug exhibits bactericidal effect and high activity against trichomonads. Vagothyl is used to treat cervical erosion, bladder diseases, and ulcers of lower extrimities.

Phenyl salicylate is a phenyl ester of salicylic acid. In intestine, this agent is cleft with formation of phenol and salicylic acid. The drug is used to treat infective diseases of bowels, bile ducts, and urinary tract.

Resorcin is a derivative of phenol. Resorcin exhibits both keratoplastic (in concentrations about 2 %) and keratolytic (in concentrations about 20 %) effects. The drug is used to treat seborrhea, eczema, herpes, ringworm, etc.

Wood tar and *ichthyol* are agents which are also containing phenol and its derivatives. These drugs are widely used to treat bacterial and parasitic skin diseases. Ointments and liniments with wood tar are used to treat eczema, psoriasis, furunculosis, etc. Wood tar is included in *Vishnevsky ointment* (tretment of wounds, burns, ulcers, and bedsores) and *Wilkinson ointment* (treatment for scab and fungal diseases).

Thymol is a phenol derivative which is included in aerosol *Hexaspray* and in pastilles *Septolete* and *Hexadreps*. These drugs are used to treat the diseases of throat and pharynx.

Dyes

Soluble dyes include such colouring agents as *brilliant green, ethacridine lactate*, and *methylene blue (Rivanol)*. Dyes occupy the intermediate position between antiseptics and chemotherapeutic drugs. Dyes have certain selectivity against microorganisms and are sometimes used for resorptive action. All agents are effective in treatment for coccal infections. The dyes are characterised by low toxicity. They affect the permeability of bacterial cell membranes which causes osmotic disbalance and lysis of microorganisms. Besides, dyes inhibit the activity of catalase, galactosidases, and other enzymes.

Brilliant green is active against staphylococci, corynebacterium diphtheriae, and other Gram-positive bacteria. This agent is used as 1–2 % alcoholic (or water) solution for the lubrication of wounds, pustular skin lesions, blepharitis, etc.

Methylene blue is characterised by less antibacterial activity than brilliant green. But the agent exhibits antimycotic activity. Ability of methylene blue to attach and release hydrogen atoms is used in the treatment of poisoning by cyanides. In this case, 50–100 ml of a 1 % solution of the drug is administered intravenously. Methylene blue transforms hemoglobin into methemoglobin. The latter substance interacts with cyanides to form non-toxic cyanmethemoglobin. Also, methylene blue is used to treat burns, cystitis, urethritis, to wash body cavities, etc.

Ethacridine lactate (Rivanol) is a bacteriostatic agent with slowly developing effect. Rivanol is used in ointments, pastes, and solutions for external application. Therapeutic indications for Rivanol are purulent wounds, burns, washing body cavities, etc. Ethacridine lactate is a non-toxic agent.

Halogen-Containing Drugs:

Chlorine-Containing Drugs

Chlorine-releasing agents are *chloramine B, chlorhexidine*, and *household bleach*. These agents have high antimicrobial activity and broad spectrum of action. Chlorine-containing drugs are active against bacteria, viruses, and amoeba. Acid-fast bacilli (e. g., *Mycobacterium tuberculosis*) are less sensitive to chlorine-containing drugs. In an aqueous environment, chlorine-containing compounds decompose with the release of atomic chlorine which interacts with cytoplasmatic proteins of microorganisms. In proteins, chlorine ions replace the hydrogen ions that makes hydrogen bond formation between polypeptide chains impossible. Due to this fact, secondary structure of proteins is disrupted. Chlorine-releasing agents also have deodorizing properties. Household bleach is used as disinfectant.

Chloramine B is used as an antiseptic. Its effect develops slowly and lasts for a long time. Chloramine B has also antimycotic activity. The agent is used to wash infected wounds, operative field, and hands. Chloramine B is also used in disinfection of instruments and rooms.

Chlorhexidine is one of the most effective antiseptics. Water and alcoholic solutions of chlorhexidine are used to sterilize instruments, wash wounds, burns, bladder, and hands. The agent is also used in room disinfection.

Iodine-Containing Drugs

Action mechanism of iodine-containing drugs is associated with interaction of N-groups of proteins with iodine. This interaction leads to coagulation of microorganism proteins. Antibacterial spectrum of iodine-containing drugs is very broad. Iodine-containing drugs are used as both antiseptics and agents for resorptive action. Thus, radioactive iodine is used in diagnostics and treatment of thyroid gland diseases. Radioactive iodine compounds are used to diagnose liver, kidney, bronchi, uterus, and vessels diseases.

Alcoholic iodine solution is used in disinfection of a surgeon's hands and an operative area, in the fungal disease treatment, and in lubrication of wounds. Besides, distracting effect of this agent is used in treatment for myositis and neuralgia.

Lugol's solution contains iodine in water solution of potassium iodide. The drug is used in mucous membranes of pharynx and larynx treatment.

Today, complex compounds of iodine with macromolecular surfactants are introduced in medicine: *Iodinol, Iodovidonum, Iodonatum*, etc. These compounds are called iodophors. Their advantage over alcoholic iodine solution is that these agents are water-soluble and have high bactericidal and absorptive activity, don't irritate skin and don't provoke the allergic reactions. Iodophores are used to cleanse mucous membranes of mouth and nasopharynx, to disinfect an operative area, treat wounds, burns, ulcers, etc.

Ioddicerinum is a mixture of iodine, dimexidum, and glycerine. The drug has a broad spectrum of antimicrobial actions. Ioddicerinum is used in the treatment of infections of skin, mucous membranes, wounds, etc., caused by *Staphylococcus*, meningococci, *Neisseria gonorrhoeae*, *Klebsiella*, *Shigella*, *Proteus*, virus of herpes and varicella zoster, *Chlamydia*, etc.

Oxidizers

Group of oxidizers contains *hydrogen peroxide* and *potassium permanganate*. Oxidizers change redox potential and therefore violate the normal physiological redox processes in microorganisms.

Under the influence of catalase, *hydrogen peroxide* decomposes with the release of molecular oxygen which exhibits low antimicrobial activity. Also, the process of decomposition is accompanied by formation of significant amount of foam. This foam washes away pus, blood clots, and dead tissue from the wounds. Therefore, hydrogen peroxide cleans the wounds. A 3% hydrogen peroxide solution is used to rins the mouth and throat, in treatment of purulent otitis media, and to stop nasal bleeding (release of oxygen accelerates the transformation of fibrinogen into fibrin).

Potassium permanganate exhibits higher antiseptic activity because it releases atomic oxigen which oxidizes biological substances. Also, potassium permanganate causes astringent, irritative, deodorant, and cauterizing effects. Potassium permanganate is used in gastric lavage in treatment of poisoning (0.02–0.1 % solutions) caused by poisons which are oxidized by potassium permanganate (e. g., morphine); in cleaning wounds, washing urethra and vagina (0.01–0.5 % water solutions); in treatment of burns (2–5 % water solutions).

Heavy Metal Compounds

Heavy metals (silver, mercury, copper, bismuth, etc.) interact with proteins of microbial cells with the formation of albuminates. Heavy metals preparations exhibit the fast and marked bactericidal effect. Some drugs have atypical for other antiseptics activity against certain microorganisms. Thus, mercury and bismuth preparations are active against *Treponema pallidum,* silver preparations – against cocci.

Mechanism of action of heavy metal preparations is the following: ions of metal interact with SH_2-groups of proteins. Inactivation of SH-containing enzymes needs significantly less metal concentrations in cells than necessary for protein coagulation. This inactivation results in disruption of bacterial cell metabolism and growth inhibition of microorganisms. Besides, heavy metal salts influence proteins of skin and mucous membranes. Depending on concentration and the type of metal, the following effects can develop on the place of drug application: astringent, irritative, or cauterizing. These effects are based on the ability of salts to interact with tissue proteins with the formation of albiminates. The interation with only superficial layers of skin and mucosa is accompanied by formation of dense albuminates preventing the penetration of ions into the deep layers of tissues. In this case, the astringent effect develops. In case of loose albuminate formation, metal ions penetrate into the deep layers of tissues that results in cauterizing effect on the tissue, accompanied by tissue damage (necrosis). Professor Schmiedeberg made up a list of metals based on albuminate density:

Pb, Al, ... Fe, Cu, Zn, ... Ag, Hg.

Metals which are located in the left part of this list have mainly astringent and irritative actions. Metals which are located in the right part of Schmiedeberg's list have cauterizing action. Metals which are located in the middle part of the list can exhibit all these actions in dependence on their concentration.

In the human organism, salts of heavy metals are distributed irregularly: most of the drug is accumulated in bones, liver, kidneys, and bone marrow. Slow ellimination of heavy metal salts is carried

out by kidneys, sweat and salivary glands, and gastrointestinal mucosa.

Silver-containing drugs are *silver nitrate*, *protargolum (silver proteinate)*, and *collargolum (colloidal silver).* These drugs have antibacterial, astringent, and anti-inflammatory actions.

Silver nitrate 1–2 % solution is used in the treatment for conjunctivitis. Silver nitrate 5–10 % solution or sticks are used in the treatment of trachoma, skin ulcers, erosion, and hypersarcosis. Protargolum and colargolum are used to treat conjunctivitis, rhinitis, urethritis, and chronic cystitis.

Zinc and copper salts have astringent, iritative, cauterizing, and antibacterial actions. *Copper sulfate* is used to treat conjunctivitis, urethritis, and vaginitis. Ophthalmic pencils with copper sulfate are used in the treatment of trachoma. Eye drops with *zinc sulfate* and *copper sulfate* are used in the treatment of conjunctivitis. Also, zinc sulfate solutions are used in the treatment for laryngitis, vaginitis, and urethritis. Zinc sulfate is the part of the dusting powders, ointments, and pastes.

Water-soluble aluminum preparations have an astringent, anti-inflammatory, and antibacterial actions. Insoluble aluminum salts have an absorptive capacity.

The preparations of lead are used as astringent and antibacterial agents in the treatment for pyderma, furunculosis, and carbuncles.

Mercuric chloride (mercury (II) chloride) and *yellow mercury oxide* are used as antiseptics. Mercuric chloride is easily soluble in water and has high antibacterial activity. The agent is used to disinfect dishes, premises, etc. Mercuric chloride isn't used to disinfect metal surfaces because it causes metal corrosion. For skin disinfection, mercuric chloride is used seldom due to high irritant effect. Eye ointment with yellow mercury oxide is used to treat conjunctivitis and keratitis.

Bismuth preparations have no astringent and cauterizing effects. Antibacterial effect of bismuth salts is manifested due to blockage of HS-groups of bacterial enzymes. Besides, bismuth exerts

an antidiarrheal effect due to its ability to bind hydrogen sulfide in the intestine. Bismuth-containing drugs (*dermatol* and *xeroform*) are used for treatment of the skin diseases (ulcers, eczema, and dermatitis). Also, bismuth-containing drugs are used to treat stomach ulcer and syphilis.

At present, heavy metal salts are used seldom.

High concentrations of heavy metal salts can cause acute poisoning with the initial excitation replaced by inhibition in the central nervous system. Simultaneously, the cardiac depression and paralytic dilation of capillaries are observed (especially caused in abdominal cavity).

Chronic poisoning may be caused due to constant intake of heavy metal salts.

The constant contact with lead or its salts can cause the chronic poisoning (saturnism) due to the accumulation of lead, mainly in bone tissue. Interaction between lead and hydrogen sulfide in the oral cavity causes formation of lead sulfide which forms the gray film on the gums. Later, blood disorders (anemia), abdominal pain attacks (lead colic), and damage to the peripheral nervous system (lead polyneuropathy) are observed. Lead polyneuropathy is characterized by a primary lesion of the motor fibers of peripheral nerves with the development of lead paralysis. The antidote – metal-complexing agent tetacinum-calcium – is used to treat lead poisoning. The drug is administered intravenously drop-by-drop. Besides, the drug is taken orally in dose 0.5 g 4 times a day. The treatment of acute lead poisoning includes subcutaneous administration of atropine sulfate solution 0.1 %, subcutaneous omnoponum, intravenous sodium bromide, and rectal delivery of magnesium sulfate.

Acute poisoning by mercuric chloride is accompanied by abdominal pain, vomiting, diarrhea, excitation of central nervous system with the following depression, and acute cardiovascular failure. In 2–4 days, the renal failure and lesions of gastrointestinal tract are observed. Unithiol is an antidote to the toxicity of mercuric chloride. The drug is administered intramuscularly or subcutaneously. Saline laxatives, activated carbon, astringent agents,

milk, and egg white are taken orally. The treatment also includes gastric lavage, forced diuresis, and hemodialysis.

Chronic poisoning by mercury salts is called mercurialism. The following are symptoms of mercurialism: disorders of central nervous system (dementia, tremor), stomatitis, anemia, etc. The treatment of chronic poisoning includes the administration of antidotes (unithiol, tetacinum-calcium, or sodium thiosulfate), the actions to remove the mercury salt from the organism, and symptomatic therapy.

Alcohols

Ethyl alcohol is used in medicine as an antiseptic and disinfectant agent. Ethanol antibacterial activity is defined due to its ability to cause dehydration and denaturation of proteins. Ethyl alcohol is used to disinfect hands of the surgeon, surgical field, and medical instruments. Disinfection of the skin is more effective if 70 % ethanol is used. Higher concentrations of ethanol have less antibacterial activity in this case because concentrated ethanol seals the epidermis that prevents its diffusion into the ducts of sweat and sebaceous glands. 20–40 % ethanol solutions significantly irritate the skin and, therefore, they are used in compresses and grinding. A 90–95 % ethanol is used to sterilize medical instruments.

Aldehydes

Formaldehyde is a water-soluble gas with a pungent irritating odor. The agent has high antibacterial activity against vegetative and spore forms of bacteria. Formaldehyde interacts with aminogroups of bacterial proteins that results in their dehydration. Formaldehyde (gas and solutions) is used to disinfect rooms, clothes, etc. Dehydrating effects of formaldehyde cause epithelial cell irritation. Mucous membranes are especially sensitive to formaldehyde. Formaldehyde affects the sweat glands and causes dry skin.

Formalin and *hexamethylenetetramine (methenamine, urotropin)* are drugs which contain formaldehyde.

Formalin is a 36.5–37.5 % water solution of formaldehyde. The drug is used to dry the skin of hands, in increased sweating of legs (0.5–1 % solutions), to sterilize instruments (0.5 %), and to preserve cadaveric material.

Urotropine converts into formaldehyde in an acidic environment. The drug is taken orally (0.05–1.0 g 5 times a day after a meal) or administered intravenously (5–10 ml of 40 % solution) for treatment of urinary tract infections. The activity of urotropin against Gram-negative bacteria is restricted. Also, hexamethylenetetramine is a part of tablets *Calcex*.

Inhalation of concentrated formaldehyde vapors can cause the acute poisoning with lacrimation, sharp cough, and the feeling of chest tightness. Oral intake of formaldehyde results in drooling, epigastric burning, gastric pain, nausea, vomiting, diarrhea, inflammation of the kidneys, loss of consciousness, and convulsions with the following inhibition of nerve centres. The treatment of poisoning includes the gastric lavage with weak *ammonia solution* and intake of covering agents (milk or egg white).

Acids and Alkalis

Antibacterial effect of acids and alkalis manifests itself due to their ability to penetrate (in the form of undissociated molecules) into bacterial cells. In bacterial cells, molecules of acids and alkalis dissociate and cause the denaturation of bacterial proteins. *Boric acid* and *salicylic acid* are used as anticeptics in medicine.

Boric acid is used to treat conjunctivitis, otitis, eczema, dermatitis, colpitis, pyoderma, etc. The following medicinal forms of boric acid are used in medicine: water, alcohol, and glycerol solutions, eye drops, ointments, pastes, and antiseptic powders for external use.

Preparations of salicylic acid have antiseptic, irritating, keratoplastic (in concentrations up to 5 %) or keratolytic (in concentrations 5–10 %) effects. Water and alcohol solutions, ointments and pastes with salicylic acid are used in the treatment of different inflammatory and infectious skin diseases. Indications for

its use include burns, blisters, warts, hyperkeratosis, excessive sweating of the feet, hair loss, psoriasis, acne vulgaris, seborrheic dermatitis, eczema, ichthyosis vulgaris, otitis media, etc.

Ammonia solution (contains 10 % ammonia) and *sodium hydrocarbonate* are alkalis that act as antiseptics. Ammonia solution is used in surgical hand antisepsis. The irritating activity of ammonia solution and ability reflexively stimulate the respiratory centre give grounds for use in syncope. Sodium hydrocarbonate solution has an expressed detergency. The drug is used to rinse mouth and throat in tonsilitis, to wash eyes, and sterilize instruments.

Table 15 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
Chlorhexidini bigluconas	For disinfection of skin or mucous membranes 0.05, 0.2, or 0.5 % solution; for disinfection of surgical field 0.5 % aqueous-alcoholic solution; for disinfection of wounds and burns 0.5 % water solution; for hand disinfection 0.5 % alcoholic or 1 % water solution	0.05 % water solution in bottles 100 ml; 20 % water solution in bottles 100 or 500 ml
Aethonium	For treatment of wounds and ulcers: 0.02–1 % solution or 0.5–2 % ointment; for treatment of keratitis, corneal ulcers, and other eye lesions: 0.1 % eye drops; for treatment of stomatitis: 0.5 % solution; for treatment of dermatitis and burns: 0.5–2 % ointment	Pouder for solution preparation; ointment 0.5 % or 1 % – 25 g
Sol. Iodi spirituosae	For external use	5 % solution in bottles 10, 15 or 25 ml
Ioddicerinum	For external use	Bottles 15 ml

Continuation of table 15

Drug name (Latin)	Single dose and mode of administration	Drug product
Spiritus aethylicus	For skin preparation 70 % solution; for processing surgical instruments 90 % solution	Bottles 100 ml
Acidum boricum	Solution or ointment for external use	2–4 % solution; 5–10 % ointment
Zinci sulfas	1–2 drops in eyes 3–4 times daily	0.25 % or 0.5 % solution of eye drops
Sol. Viridis nitentis spirituosae	For external use	1 % or 2 % spirituous solutions
Furacilinum	Orally 0.1 g 4 times a day; ointment for external use; solutions for washing infected cavities and mucous membranes	Tablets 0.1 g (for oral intake); tablets 0.02 g (for preparation of solutions); ointment 0.2 % – 25 g; water solution 1:5 000 (1 part of furacilinum to 5 000 parts of water); alcoholic solution 1:1 500
Sol. Hydrogenii peroxydi diluta	For external use	3 % solution in bottles 50 ml
Kalii permanganas	0.1–0.5 % solution for processing of wounds; 2–5 % solution for processing of burns; 0.02–0.05 % solution for gastric lavage	Solutions with different concentrations
Aethacridini lactas	Solutions, ointment and aspersion for external use	0.1 % or 0.2 % solutions; 3 % ointment; 3 % aspersion; 5–10 % paste
Unithiolum	Intramuscularly 0.25–0.5 g 2–4 times daily	Ampoules 5 ml of 5 % solution

Step 1. Tasks for Self-Control
Antiseptics and Disinfectants

1. To prepare an operative field a doctor used dichlorinated biguanid derivative. It is the most active local antiseptic, that shows fast and strong bactericidal action on Gram-negative and Gram-positive bacteria. What drug is this?

A. Unithiol.
B. Brilliant green.
C. Furacilinum (nitrofural).
D. Chloramine.
E. Phenasalum.

2. For the processing of the burn surface of the patient's skin a specific drug was used. Its antiseptic properties are provided by free oxygen that reacts with organic substances. What drug is this?

A. Potassium permanganate.
B. Furacilinum.
C. Chlorhexidine bigluconate.
D. Boric acid.
E. Sodium hydrocarbonate.

3. Profuse foam appeared when dentist put hydrogen peroxide on the mucous membrane of the oral cavity. What enzyme caused such activity?

A. Cholinesterase.
B. Catalase.
C. Glucose-6-phosphate dehydrogenase.
D. Acetyltransferase.
E. Methemoglobin reductase.

4. A patient with mercury poisoning was admitted to the toxicological department from the chemical industry. What drug should be used?

A. Naloxone.
B. Enterosorbent.
C. Isonitrosine.
D. Unithiol.
E. Activated carbon.

5. A patient with abscess of the cat wound applied to the traumatological department. The wound was washed with 3 % hydrogen peroxide to be cleaned from the pus. Foam was not observed. What caused inefficiency of the drug?

A. Pus in the wound.

B. Shallow wound.

C. Low concentration of H_2O_2.

D. Inherited insufficiency of erythrocyte phosphate dehydrogenase.

E. Inherited insufficiency of catalase.

6. A patient working at a chemical plant was admitted to the toxicological department with mercury poisoning. What medicine should be used?

A. Unithiol.

B. Enterosorbent.

C. Activated carbon.

D. Naloxone.

E. Isonitrosine.

7. A 38-year-old man who poisoned himself with mercuric chloride was taken to the admission room in grave condition. What antidote should be immediately introduced?

A. Atropine.

B. Nalorphine.

C. Unithiol.

D. Isonitrosine.

E. Dipiroxime.

8. A patient has applied to doctor with complaints of multiple purulent rashes on the skin of extremities. What antiseptic should be prescribed to him?

A. Alcoholic solution of iodine.

B. Insulin.

C. Prednisolone.

D. Sibazon.

E. Heparin.

CHEMOTHERAPEUTIC DRUGS
ANTIBIOTICS

Paul Ehrlich is the founder of the modern chemotherapy. In 1907, he suggested the first effective agent for syphilis treatment – salvarsan. In 1932, Gerhard Domagk discovered the antibacterial properties of red streptocid.

The first antibiotic penicillin was discovered by Sir Alexander Fleming in 1929. In 1940, Sir Howard Walter Florey and Ernst Boris Chain produced a pure form of penicillin. In the USSR, the pure penicillin was produced by Z. V. Yermolyeva and T. I. Balyazina in 1942. The significant amount of natural and synthetic antibacterial drugs has been created in succeeding years. The synthesis of new antibacterial drugs is presently going on.

Chemotherapeutic drugs are characterized by definite spectrum of antibacterial action. One of the requirements for drugs is their low toxicity for humans and animals.

There are the following main principles of chemotherapy.

1. It is necessary to make the precise diagnosis and identify the pathogen and its antibiotic sensitivity.
2. It is necessary to start treatment as early as possible, yet the number of causative agent is low and the serious lesions of internal organs do not develop.
3. The route of drug administration should be optimal that provides the best drug – pathogen interaction.
4. The drug concentration in human organism should be effective and stable throughout the whole therapy. Sometimes, the knockout dose is prescribed in early treatment to create a necessary effective concentration of the antibacterial agent.
5. The duration of antibacterial therapy should be optimal (the therapy lasts 3–5 days after clinical recovery.
6. The measures to support the body's defences should be provided together with chemotherapy (vitamins, immunomodulators, drugs that support the hepatic and renal functions, etc.).

Chemotherapeutic drugs include the following drug groups:

1) antibiotics;

2) sulfonamides;

3) synthetic antibacterial drugs with different chemical structure (quinolones, fluoroquinolones, hydroxyquinolines, nitroimidazole derivatives, and nitrofurane derivatives);

4) antifungal drugs;

5) antiviral drugs;

6) antiprotozoal drugs;

7) antisyphylitic drugs;

8) antituberculosis drugs;

9) anthelmintic drugs.

Antibiotics are drugs of bacterial origin and their semi-synthetic analogues which selectively damage or kill certain microbial species. Antibiotics are classified according to their origin, chemical structure, mechanism of action, and character of the influence upon bacteria.

Antibiotic classification according to chemical structure is the following:

1) β-lactam antibiotics: penicillins, cephalosporins, carbapenems, and monobactams;

2) antibiotics containing the macrocyclic lactone rings in molecules: macrolides and azalides;

3) tetracyclines (antibiotics containing four condensed six-membered rings in molecules);

4) chloramphenicol drug group;

5) aminoglycosides (antibiotics containing the aminosugars in molecules);

6) polypeptides (polymyxins and gramicidin C);

7) polyenes (amphotericin B, nystatin, and levorin);

8) glycopeptides (vancomycin and ristomycin);

9) lincosamides (lincomycin and clindamycin);

10) ansamycins (rifampicin and rifamycin);

11) antibiotics with steroidal structure (sodium fusidate);

12) different antibiotics (fusafungine).

According to mechanism of action, antibiotics are classified into the following groups:

1) antibiotics affecting the synthesis of bacterial cell wall: β-lactams and glycopeptides;

2) antibiotics affecting the function of bacterial cytoplasmic membrane: polypeptides and polyenes;

3) antibiotics affecting the synthesis of bacterial proteins: aminoglycosides, tetracyclines, chloramphenicols, macrolides, and lincosamides;

4) antibiotics affecting the synthesis of nucleic acids: ansamycins.

There are two types of antibacterial action of antibiotics: bactericidal and bacteriostatic. Bactericidal antibiotics affect the synthesis of bacterial cell wall or the function of cytoplasmic membrane; these agents kill the bacteria. Bactericidal antibiotics include β-lactams, glycopeptides, polypeptides, and polyenes. Besides, high doses of aminoglycosides, chloramphenicol, and rifampicin are cases of bactericidal action. Tetracyclines, macrolides, ansamycins, lincosamides, etc. have the bacteriostatic effect. Bacteriostatic antibiotics affect the growth and division of bacteria.

Depending on the number of bacteria species affected by a drug, antibiotics are divided into the drugs of broad spectrum and the agents of narrow spectrum. The antibiotics of broad spectrum of antibacterial activity include tetracyclines, chloramphenicol, aminoglycosides, cephalosporins, and semisynthetic penicillins, azalides, and macrolides. Narrow spectrum is typical for biosynthetic penicillins, macrolides, lincosamides (these groups are active against Gram-positive bacteria), and polymyxines (active against Gram-negative flora).

β-Lactam Antibiotics

It is the dominant group of modern antibiotics which includes penicillins, cephalosporins, carbapenems, and monobactams. β-lactams are bactericidal antibiotics. Their mechanism of action is associated with inhibiting cell wall synthesis due to the blockage of transpeptidase (an enzyme that cross-links the peptidoglycan chains to form rigid cell walls). It results in lysis of bacterial cells.

Penicillins

Penicillins are a type of antibiotics that contain the 6-aminopenicillanic acid in the molecules. Natural penicillins are produced by *Penicillium* molds. The semisynthetic penicillins are synthezied due to chemical modification of 6-aminopenicillanic acid.

Penicillins are classified as follows.

1. Biosynthetic penicillins.

1.1. Drugs for parenteral administration:

– short-acting penicillins: *benzylpenicillin sodium* and *benzylpenicillin potassium*;

– long-acting penicillins: *benzylpenicillin novocaine salt, bicillin-1,*and *bicillin-5.*

1.2. Drugs for enteral administration: *phenoxymethylpenicillin*.

2. Semisynthetic penicillins.

2.1. Drugs for both parenteral and enteral administration:

– drugs stable to penicillinase: *oxacillin* and *nafcillin*;

– drugs of broad spectrum (aminopenicillins): *ampicillin* and *amoxicillin*.

2.2. Drugs of broad spectrum for parenteral administration:

– carboxypenicillins: *carbenicillin disodium* and *ticarcillin*;

– ureidopenicillins: *azlocillin, piperacillin,* and *mezlocillin*.

2.3. Drugs for enteral administration of broad spectrum:

– carboxypenicillins: *carbenicillin indanyl sodium* and *carfecillin*.

Biosynthetic Penicillins

Biosynthetic penicillins are drugs of narrow antibacterial spectrum which include mainly Gram-positive bacteria. The following bacteria are sensitive to biosynthetic penicillins: staphylococci, streptococci, pneumococci, gonococci, meningococci, *Clostridia* (the causative agents of gas gangrene and tetanus), *Corynebacterium diphtheriae*, *Bacillus anthracis*, spirochetes (the causative agents of syphilis, relapsing fever, and leptospirosis), and actinomycetes.

Benzylpenicillin sodium and *benzylpenicillin potassium* are the water-soluble salts of monobasic acid. In case of oral intake, these drugs are dystroyed by hydrochloric acid, therefore they are administered parenterally, mainly intramuscularly. Duration of benzylpenicillin action is 3–4 hours, therefore drugs are administered 6 times a day. In special cases, benzylpenicillin is administered intravenously, intra-arterially, into the spinal canal (only sodium salt), joint capsules, and serous cavities, or it is used in inhalations. Nearly 60–70 % of administered benzylpenicillin is excreted through kidneys in non-modified form. Insignificant part of the drug is secreted into biliary ducts and excreted through intestine. The rate of drug elimination depends on renal and hepatic functions. The elimination of benzylpenicillin in patients with simultaneous damage of renal and hepatic functions can be slowed down 10 times.

There are benzylpenicillin preparations of prolonged action: *benzylpenicillin novocaine, bicillin-1*, and *bicillin-5*. Water suspensions of these drugs are administered intramuscularly. Benzylpenicillin novocaine is administered twice a day, bicillin-1 – once in 1–2 weaks, and bicillin-5 – once a month. Long-acting drugs are prescribed only if it is known that a patient has no allergy to penicillins and causative agent has high sensitivity to a prescribed drug. Therapeutic indications for the long-acting biosynthetic penicillins are rheumatism and syphilis.

Phenoxymethylpenicillin is an acid-stable penicillin because its molecules contain the phenoxymethyl groups. Antibacterial spectrum of phenoxymethylpenicillin is identical to antibacterial

spectrum of benzylpenicillin. The drug is easily absorbed in gastrointestinal tract but its blood concentration is not high. Therefore, phenoxymethylpenicillin is not used in treatment of severe infections. The drug is prescribed for oral intake 4–6 times a day for the teatment of mild to moderate infections, such as pharyngitis, tonsillitis, sinusitis, otitis, bronchitis, pneumonia, erysipelas, erysipeloid, erythema migrans, lymphadenitis, lymphangitis, scarlet fever, etc.

Semisynthetic Penicillins

Semisynthetic penicillins are synthesized by the acylation of 6-aminopenicillanic acid.

Oxacillin and *nafcillin* are known as antistaphylococcal penicillins. The antibacterial spectrum of these drugs is similar to the spectrum of benzylpenicillin. But these drugs are stable to penicillinase action, therefore they are highly active against different strains of *Staphylococci*, including penicillinase producing strains.

Oxacillin is taken orally or administered parenterally 4–6 times a day. The degree of drug binding to plasma proteins is 90–95%. Oxacillin does not penetrate through the blood-brain barrier. The main route of the drug excretion is kidneys.

Nafcillin has high antibacterial activity. Nafcillin is administered both orally and parenterally. The drug easily penetrates through the blood-brain barrier. The drug is mainly excreted with bile.

Ampicillin and *amoxicillin* are aminopenicillins. The drugs have the broad spectrum of antibacterial action but are broken by penicillinase. The spectrum of antibacterial action of aminopenicillins includes Gram-positive and Gram-negative bacteria. Aminopenicillins are active against *Enterococcus*, *Salmonella*, *Shigella*, *Escherichia coli*, some strains of *Proteus*, etc. It is significant that activity of aminopenicillins against Gram-positive bacteria is 3–4 times less than the activity of biosynthetic penicillins. But their activity against Gram-negative bacteria is higher than the activity of tetracyclines and

chloramphenicol. Aminopenicillins are not active against *Pseudomonas aureginosa*.

Ampicillin is an acid-stable antibiotic which is easily absorbed in gastro-intestinal tract. The degree of binding to plasma proteins is low. The drug is excreted from the body through the kidneys and liver and creates the high concentration in urine and bile. This allows its use in the treatment for infections of urinary and biliary tracts. Ampicillin badly penetrates through the blood-brain barrier. The drug is taken orally 3–4 times a day or administered intramuscularly 4–6 times a day. Toxicity of ampicillin is low.

Amoxicillin is similar to ampicillin. But the drug is better absorbed in gastrointestinal tract with high concentrations in plasma and tissues.

There are co-formulated penicillin preparations such as *Ampiox* (combination of ampicillin with oxacillin in ratio 2:1).

Carbenicillin is a broad-spectrum semisynthetic penicillin of carboxypenicillin group. The drug is active against many Gram-positive and Gram-negative bacteria including *Pseudomonas aureginosa*, *Proteus*, and some bacteroides. Beta-lactamase breaks up carbenicillin, therefore it does not influence staphylococci producing penicillinase. Carbenicillin is used mainly as a reserve antibiotic in treatment of infectious diseases caused by *P. aureginosa*.

Carbenicillin is an acid-labile antibiotic, therefore it is administered intramuscularly or intravenously. The drug permeability through the blood-brain barrier is low. The main route of excretion is through the kidneys. Duration of carbenicillin action is 4–6 hours. Carbenicillin indanyl sodium is an acid-stable form of carbenicillin which is administered orally mainly in treatment of urinary tract infections.

Ticarcillin is carboxypenicillin with high activity against *Pseudomonas aureginosa*. The drug is administered parenterally. Such carboxypenicillins as carfecillin and carindacillin are to be given orally. Their bioavailability in oral intake is above 40 %.

A group of ureidopenicillins includes such medications as *azlocillin, mezlocillin,* and *piperacillin*. Ureidopenicillins are characterized by high activity against *P. aureginosa* and fast development of bacterial resistance. These drugs are administered only parenterally 3 times a day.

There are inhibitors of β-lactamases that prevent the destruction of penicillins by penicillinase: *clavulanic acid*, *sulbactam*, and *tazobactam*. These agents are used in combination with penicillins. For example, *Augmentin* consists of amoxicillin and clavulanic acid. The drug is administered once a day for treatment of infectious diseases of respiratory and urinary tracts, joints, bones, sepsis, etc. Another group of combination drugs includes *Unazinum* (ampicillin with sulbactam), *Co-amoxiclav* (amoxicillin with clavulanic acid), and *Tazocin* (piperacillin with tazobactam).

Despite low toxicity and inability to accumulate in the organism, penicillins have many side effects.

Allergic reactions (skin rash, bronchospasm, and anaphylactic shock) are the most common side effect of penicillins. To prevent allergy, the test for sensitivity to penicillins shoud be performed before the drug administration. In the case of anaphylactic shock, intramuscular adrenaline, intravenous glucocorticoids and calcium chloride must be administered very quickly.

Other side effects of penicillins are painful injections, infiltrates, and aseptic necrosis in the injection site. Oral drug intake can cause nausea, diarrhea, stomatitis, and glossitis. Intravenous administration can cause phlebitis and trombophlebitis. Large doses of penicillins or their use in patients with renal failure can result in development of neurotoxic effects. Sometimes, penicillins cause disturbances of cardiac activity and inhibition of hepatic enzymes. Semisynthetic broad-spectrum penicillins can cause disbiosis and superinfection.

Cephalosporins

Cephalosporins are semisynthetic antibiotics with β-lactam ring in molecules. Mechanism of cephalosporins' action is associated with affection of bacterial cell wall synthesis due to inhibition of transpeptidase. Cephalosporins have the bactericidal effect and are broad-spectrum antibiotics. The drugs are stable to staphyloccocal β-lactamase, but β-lactamases of Gram-negative bacteria can affect some cephalosporins.

Cephalosporins are grouped into four generations.

1. Cephalosporins, 1st generation.

1.1. Drugs for parenteral administration: *cephaloridine, cefalotin, cefazolin, cefradine,* and *cefapirine.*

1.2. Drugs for enteral use: *cephalexin, cephradine,* and *cefadroxil.*

2. Cephalosporins, 2nd generation.

2.1. Drugs for parenteral administration: *cefamandole, cefuroxime, cefoxitin, cefmetazole,* and *ceforanide.*

2.2. Drugs for enteral use: *loracarbef, cefaclor,* and *cefuroxime.*

3. Cephalosporins, 3rd generation.

3.1. Drugs for parenteral administration: *cefoperazone, cefotaxime, ceftriaxone, ceftazidime,cefmenoxime,* and *moxalactam.*

3.2. Drugs for enteral use: *cefixime, ceftibuten,* and *cefpodoxime.*

4. The 4th generation cephalosporins are the drugs for parenteral administration: *cefepime, cefpirome, cefclidine,* and *cefozopran.*

First Generation Cephalosporins

First generation cephalosporins are antibiotics with high activity against Gram-positive bacteria. Also, some Gram-negative bacteria are sensitive to these drugs. Antibacterial spectrum of 1st generation cephalosporins includes staphylococci, streptococci, pneumococci, meningococci, gonococci, *Proteus mirabilis*, *Escherichia coli,*

Corynebacterium diphtheriae, Clostridium, Klebsiella pneumoniae, Salmonella, Shigella, and actinomycetes. First-generation cephalosporins have no activity against methicillin-resistant staphylococci, *Pseudomonas*, indole-positive *Proteus, Bacteroides, Enterococcus, Enterobacter*, etc.

Therapeutic indications for 1st generation drugs are infectious diseases of respiratory tract, pneumonia, peritonitis, osteomyelitis, otitis, furunculosis, infected wounds, infections of urinary tract, prevention of surgical infections, etc.

Cefazolin is 1st generation cephalosporin for parenteral administration. The drug is administered intramuscularly or intravenously 3–4 times a day. Cefazolin has high antibacterial activity and penetrates in the tissues better than other 1st generation drugs. The high drug concentration is created in bile and urine. The nephrotoxicity of cefazolin is low. There are the following side effects of the drug: superinfection caused by *Candida* or *Pseudomonas aeruginosa*, allergic reactions, leukopenia, pain and infiltrations in the injection site.

Cephalexin is easily absorbable in the gastrointestinal tract. The drug is taken orally 4 times a day. Cephalexin is available in the following medical forms: capsules, tablets and suspension for oral intake. The drug is used to treat infectious diseases of moderate severity. Side effects of cephalexin are as follows: dysbiosis and leukopenia.

Second Generation Cephalosporins

The antibacterial spectrum of 2nd generation cephalosporins is similar to the 1st-generation cephalosporins. But 2nd-generation has higher activity against Gram-negative bacteria and it is less active against Gram-positive flora. These drugs are not active against *Pseudomonas aeruginosa*. Second generation cephalosporins are used to treat infectious diseases of respiratory tract, abdominal and gynecological infections, septicemia, endocarditis, urinary tract infections, infections of bones, joints, skin and soft tissues, to prevent postoperative infections.

Cefoxitin is active against bacteroids. It is highly active against other Gram-negative bacteria (*Escherichia coli, Haemophilus influenzae, Salmonella, Shigella, Proteus mirabilis*, gonococci). Cefoxitin is also active against Gram-positive bacteria (*Staphylococcus*, *Streptococcus*) and against some anaerobic bacteria. The drug is resistant to β-lactamase. *Pseudomonas aeruginosa, Listeria,* many strains of enterococci and methicillin-resistant staphylococci, and others are insensitive to cefoxitin. The drug is administered intramuscularly or intravenously 2–3 times a day.

Cefaclor is the 2nd generation cephalosporin for peroral use. The drug is taken orally 3 times a day. The drug is highly active against Gram-negative bacteria (*Escherichia coli, Haemophilus influenzae, Salmonella, Shigella, Proteus mirabilis, Klebsiella, Neisseria gonorrhoeae, Citrobacter*). Besides, cefaclor is active against Gram-positive bacteria. The drug has no activity against anaerobic microorganisms (*Bacteroides*, etc.), *Pseudomonas*, *Enterococcus*, *Listeria*, *Serratia*, etc.

Cefuroxime is available both for peroral and parenteral administration. The drug has a higher ability to penetrate through the blood-brain barrier than other drugs of the 2nd generation, and it is used to treat meningitis. The drug is administered parenterally or taken orally 2–3 times a day.

Third Generation Cephalosporins

Antibacterial spectrum of these drugs is wider, and their activity against Gram-negative bacteria is higher compared to preceding drugs. Third generation cephalosporins are stable to Gram-negative β-lactamases. *Ceftazidime, cefotaxime*, and *cefoperazone* are active agaisnt *Pseudomonas aeruginosa*.

All third generation cephalosporins (except cefoperazone) easily penetrate into tissues, including central nervous system. Most of the drugs are excreted through the kidneys in unchanged form. Only ceftriaxone and cefoperazone are excreted mainly with bile. Therapeutic indications for the third generation cephalosporins are

infections of respiratory tract, bones, soft tissues, abdominal cavity, and urinary tract, sepsis, meningitis, endocarditis, etc. The drugs should be taken 2–3 times a day, but ceftriaxone and cefoperazone – 1–2 times a day.

Fourth Generation Cephalosporins

All forth-generation cephalosporins are administered only parenterally. These drugs have the extended antibacterial spectrum and high activity against both Gram-positive and Gram-negative bacteria. These drugs have a greater resistance to β-lactamases than the 3rd generation cephalosporins. Fourth generation cephalosporins affect bacteria insensitive to other antibiotics (including carbapenems). It is due to drug ability to penetrate through cell membranes and to bind to bacterial penicillin-binding proteins. Besides, the 4th generation cephalosporins create high concentrations in periplasmic space. But these drugs are inactive against bacteroides, therefore, for expansion of antibacterial spectrum, they are combined with metronidazole, carboxypenicillins, and ureidopenicillins. Secondary resistance of bacteria to these drugs develops slowly. The therapeutic indications for the 4th generation cephalosporins are infections of respiratory and urinary tracts, sepsis, surgical infections, meningitis, etc. Cefepime and cefpirome are administered twice a day.

Therapy with cephalosporins may be accompanied by allergic reactions. Cephalosporins are contraindicated to patients with allergy to penicillins in anamnesis. Nephrotoxicity is typical mainly for the 1st-generation cephalosporins. Neurotoxicity (hallucinations, convulsions, nystagmus) is due to antagonism between cephalosporins and γ-aminobutyric acid. Hematotoxicity (leukopenia, thrombocytopenia, neutropeniza) can develop in patients with renal failure or in the case of parenteral administration of high doses of cephalosporins. Therapy by cephalosporins can be accompanied by elevated liver enzymes in blood. Enteral cephalosporin intake can cause disbiosis. Patients treated with cephalosporins should avoid alcohol consumption because the drugs

have Antabuse-like effect. In this case, alcohol intake can result in nausea, vomiting, diarrhea, tachycardia, etc.

Monobactams

Monobactams are β-lactam antibiotics which are active only against aerobic Gram-negative bacteria (e. g., *Escherichia coli, Enterobacter, Neisseria, Pseudomonas, Proteus, Serratia, Morganella, Salmonella, Shigella, Klebsiella,* etc.).

The representative of monobactams is *aztreonam*. The drug has high stability to β-lactamases of Gram-negative bacteria, but it is destroyed by β-lacatamases of Gram-positive microorganisms. Thus, aztreonam has no activity against Gram-positive bacteria, bacteroides, and other anaerobes. The therapeutic indications of aztreonam are severe infections of urinary and respiratiry tracts, abdominal cavity, soft tissues, meningitis, sepsis, etc. The drug is administered intramuscularly or intravenously 2–3 times a day. The side effects of aztreonam are allergic reactions, dysbiosis, dyspepsia, and phlebitis.

Carbapenems

It is a modern group of β-lactam antibiotics with high stability to β-lactamases and broad antibacterial spectrum. Carbapenems are active against both Gram-positive and Gram-negative aerobic and anaerobic bacteria, including *Pseudomonas aeruginosa*. The mechanism of carbapenems' action is identical to other β-lactam antibiotics. These drugs are divided into two generations:

– 1st generation: *imipenem, tienam, primaxin*;

– 2nd generation: *meropenem*.

Imipenem is a semisynthetic antibiotic with broad spectrum of action. The drug is stable to β-lactamases but is destroyed by dehydropeptidase-I (enzyme of proximal tubules of nephron). *Tienam* and *primaxin* are co-formulated drugs which contain imipenem and cilastatin in ration 1:1. Cilastatin is inhibitor of dehydropeptidase-I.

Meropenem is stable to dehydropeptidase-I, therefore it does not require the combination with cilastatin. Also, antibiotic is stable to β-lactamase action. Antistaphylococcal activity of meropenem is 2–4 times less than the activity of tienam. On the other hand, the drug activity against Gram-negative enterobacteria and Pseudomonas is higher 2–8 times.

There are microorganisms with natural resistance to carbapenems. They are *Chlamydia*, *Mycoplasma*, *Corynebacterium*, *Mycobacterium*, *Flavobacterium*, methicillin-resistant staphylococci, fungi, and protozoa.

Carabapenems are administered only parenterally. Tienam is administered intravenously 4 times a day or intramascularly 2 times a day. Meropenem is administered intravenously 3 times a day. Carbapenems are reserve antibiotics which are used in treatment of severe infections in case of ineffectiveness of other antibiotics. There are the following therapeutic indications for carbapenems:

– intraperitoneal surgical infections;

– gynecological infections after labor, cesarean section, and surgery;

– intensive therapy for newborns;

– complicated infections of urinary tract;

– complicated infections of bones, joints, skin, and soft tissues;

– sepsis;

– pulmonary infections;

– infectious diseases in patients with neutropenia;

– meningitis (meropenem is a drug of choice due to higher permeability through the blood-brain barrier and less neurotoxicity).

Side effects of carbapenems are as follows:

– pain, thrombophlebitis, and sealing the injection site;

– allergic reactions;

– superinfections;

– nephrotoxicity (more common for imipenem);

– neurotoxicity: tremor, muscular hypertone, paresthesia, encephalopathy, convulsions (in the case of intravenous administration of tienam or primaxin, but not meropenem).

Macrolides and Azalides

Macrolides are antibiotics containing macrocyclic lactone rings in molecules.

There are three generations of macrolides:

– 1st generation: *erythromycin* and *oleandomycin*;

– 2nd generation: *clarithromycin, roxithromycin, spiramycin,* and *midecamycin*.

– 3rd generation (azalides): *azithromycin*.

Mechanism of macrolide action is as follows. Drugs bind to 50S ribosomal subunit that results in violation of ribosome translocation along mRNA and inhibition of protein synthesis. The macrolides are bacteriostatic antibiotics.

First-generation macrolides are drugs with narrow antibacterial spectrum. These drugs are active mainly against Gram-positive bacteria (streptococci, staphylococci, pneumococci, *Corynebacterium diphtheriae*, etc.). Besides, gonococci, *Mycoplasma*, *Chlamydia*, *Legionella*, spirochetes, certain strains of *Brucella* and *Mycobacteria* are sensitive to 1st-generation macrolides. But most Gram-negative microorganisms have high resistance to these drugs.

The second- and third-generation macrolides have the broad antibacterial spectrum. These drugs are active against enterococci, *Escherichia coli*, *Haemophilus influenzae*, *Shigella*, *Salmonella*, *Bacteroides*, *Helicobacter pylori*, etc. Azithromycin has high activity against bacteria – causative agents of genital infections (*Neisseria gonorrhoeae*, *Chlamydia*, spirochetes, and *Trichomonas vaginalis*).

Macrolide resistance of bacteria develops readily, therefore a course of treatment should not exceed 7 days.

Erythromycin is a low toxic antibiotic for oral intake. The drug is slowly absorbed in gastrointestinal tract. Erythromycin is partly degraded by gastric juice, therefore the drug is used in capsules or specially-coated tablets. The bioavailability of erythromycin is higher if taken before a meal. The drug esealy penetrates into tissues and body fluids (except central nervous system). High concentrations of the drug are created in lungs, liver,

prostate, and urinary tract. About 60–70 % of the administered dose undergo hepatic metabolism. Erythromycin is taken 4–6 times a day before a a meal or used locally in ointments. Erythromycin phosphate is used in intravenous administration 2–3 times a day in a dose of 0.2 g.

Oleandomycin has lower antibacterial activity than erythromycin, but irritative ability of oleandomycin is higher. The drug is taken orally 4 times a day. Presently, oleandomycin is not used in monotherapy. It is most commonly combined with tetracyclines (oletetrin, tetraolean, etc.).

Clarithromycin is 2–4 times more active against staphylococci and streptococci than erythromycin. The drug is used in treatment of infectious diseases caused by *Mycoplasma*, *Chlamydia*, *Toxoplasma*, and *Helicobacter pylori*. Clarithromycin is easily absorbed in gastrointestinal tract. The drug undergoes hepatic metabolism and is excreted through the kidneys. Clarithromycin is taken 2 times a day. Course of treatment is 5–14 days. Side effects are abdominal pain, diarrhea, and nausea.

In comparison with the 1st and 2nd generations, molecules of the 3rd-generation macrolides have aromatic group in the structure of macrocyclic lactone ring, and due to this they have new properties. In contrast with erythromycin, *azithromycin* is 2–4 times less active against Gram-positive cocci. But drug activity against Gram-negative bacteria is higher. The bioavailability of azithromycin in gastrointestinal tract is low. The drug can accumulate in the cells (intracellular concentration may be higher than plasma concentration 10–100 times). Azithromycin does not penetrate through the blood-brain barrier. The drug is excreted through the kidneys in unchanged form. Azithromycin is taken orally once a day. The first dose is twice higher than subsequent doses. Therapeutic indications for azithromycin are bronchitis, otitis, sinusitis, erysipelas, mastitis, whooping cough, diphtheria, chlamydial conjunctivitis, chlamydial pneumonia of newborns, pneumonia caused by *Mycoplasma pneumoniae*, lobar pneumonia caused by *Legionella pneumophila* and *Moraxella catarrhalis*, primary syphilis, gonorrhea,

cholecystitis, enteritis, colitis, toxoplasmosis, urogenital infections, and ulcer diseases of stomach and duodenum.

New macrolide antibiotic *josamycin* is approved in medicine. The drug has broad antibacterial spectrum and causes bacteriostatic or bactericidal (in high doses) effect. The resistance of bacteria to josamycin develops seldom.

Tetracyclines

Tetracyclines are antibiotics with four condensed 6-member cycles in molecules. A classification of tetracyclines is as follows:

1) biosynthetic tetracyclines: *oxytetracycline, tetracycline,* and *demeclocycline;*

2) semisynthetic tetracyclines: *metacycline (rondomycine), doxycycline (vibramycin),* and *minocycline*.

The antibacterial spectrum of tetracyclines is broad and includes such microorganisms as Gram-positive and Gram-negative cocci, *Escherichia coli*, *Chlamydia*, *Rickettsia*, *Mycoplasma*, *Ameba*, *Plasmodium*, *Helicobacter pylori*, *Klebsiella*, *Enterobacter*, Spirochaetales, *Vibrio cholerae*, *Yersinia pestis*, *Francisella tularensis*, *Brucella*, *Shigella*, *Salmonella*, etc. Tetracyclines have no activity against *Proteus*, *Pseudomonas aeruginosa*, viruses, and fungi. Bacterial resistance to tetracyclines develops slowly and can be characterized by cross-resistance.

Tetracyclines block protein synthesis in bacterial cells. The drugs bind to 30S ribosomal subunits and affect the binding of tRNA to them, that stops protein synthesis. Besides, tetracyclines form the compounds with biologically active two valence metals (iron, calcium, zink, etc.). Tetracyclines have the bacteriostatic effect.

Tetracyclines are liposoluble agents, therefore they are easily absorbed in gastrointestinal tract. Also, tetracyclines easily penetrate through tissue barriers and accumulated in the tissues. It is necessary to notice that the drug permeability into mother's milk and amniotic fluid is better than into the skin, cerebrospinal fluid, and saliva. The degree of binding to proteins for biosynthetic tetracyclines is 20–40 % and for semisynthetic drugs – 60–95 %. Tetracyclines

undergo partial biotransformation in the liver and are excreted with urine and bile. The drugs are taken orally. Their absorption is higher if the drug is taken 1–1.5 hours before a meal or 3 hours after a meal. It is necessary to notice that milk significantly reduces the absorption of tetracyclines due to formation of complexes between the drug and two valence metals. Semisynthetic tetracyclines are less capable to form such compounds, therefore their bioavailability at oral intake is closer to 100 %. Oxytetracycline and tetracycline are also used in ointments. Tetracycline is administered intramuscularly, and doxycycline – intravenously. Oxytetracycline and tetracycline are prescribed to take 4 times a day, methacycline – 2–3 times, doxycycline and minocycline – 1–2 times, and demeclocycline – once a day.

Therapeutic indications for tetracyclines are as follows: putrid fever, Q fever, trachoma, psittacosis, ornithosis, urogenital chlamydiosis, dysentery, leptospirosis, plague, brucellosis, tularemia, anthrax, cholera, bronchitis, pneumonia, tonsilitis, otitis, sinusitis, infections of urinary and biliary tracts, osteomyelitis, syphilis, gonorrhea, ulcer diseases of stomach and duodenum (doxycycline), intestinal amebiasis, etc.

Presently, *tigecycline*, a new tetracycline derivative, is approved in medicine. The drug has high activity against Gram-positive and Gram-negative bacteria. Tigecycline is used as a reserve antibiotic when other antibiotics are ineffective. The drug is administered intravenously, drop-by-drop, twice a day.

It is necessary to notice that tetracyclines affect cell division both in microorganisms and in a human organism. Due to this, drugs affect the epithelization of the intestine (dyspesia, erosions, ulcers, glossitis) and the skin (dermatitis, photosensitization) and suppress the hemopoiesis (leukopenia, anemia, thrombocytopenia). Catabolic effect of tetracyclines results in inhibition of protein synthesis and immunity.

Tetracyclines are hepatotoxic and teratogenic drugs.

Tetracyclines form the chelates with calcium phosphate in teeth and bones that results in the delay of skeletal growth in children,

yellow coloration of teeth, violation of tooth enamel formation, and caries. Due to this, tetracyclines are contraindicated in children aged under 12 years, pregnant woman, and nursing mothers.

Expired tetracyclines form toxic substances. In this case, the following intake of expired tetracyclines causes an acute kidney injury (Fanconi's syndrome).

Tetracycline in young children can cause the increase of intracranial pressure along with development of meningeal symptoms (headache, vomiting, etc.).

Tetracyclines can cause dysbiosis, hypovitaminosis B, candidiasis, and enterocolitis. Fast intravenous administration of doxycycline can cause the development of acute heart failure. Minocycline causes vestibular disturbances. Tetracycline therapy can cause allergic reactions.

Chloramphenicol Group

Levomycetin (chloramphenicol) is the main representative of this group. Such drugs as levomycetin, levomycetin stearate, levomycetin palmitate, and levomycetin succinate are the most commonly used in medicine.

Levomycetin inhibits the protein synthesis in bacterial cells due to binding to 50S subunit of ribosomes. Also, the drug inhibits peptidyl transferase activity that impedes prolongation of polypeptides. Chloramphenicol has a bacteriostatic effect.

Levomycetin is a broad-spectrum antibiotic. Unfortunately, practical realization of the drug potential in medicine is impossible due to high drug toxicity. Therefore, levomycetin is used as a reserve antibiotic. Levomycetin inhibits the growth of the most strains of staphylococci, pneumococci, streptococci, meningococci, *Haemophilus influenzae*, *Brucella*, *Rickettsia*, *Chlamydia*, *Mycoplasma*, *Vibrio cholerae*, *Escherichia coli*, *Shigella*, *Salmonella*, and *Enterobacter*. It is important that chloramphenicol inhibits the growth of such anaerobes as bacteroides, anaerobic cocci, and fusobacteriales. The resistance of bacteria to chloramphenicol develops slowly.

Levomycetin is prescribed mainly for oral intake. Levomycetin succinate is administered intravenously (seldom – intramuscularly or in the form of an aerosol in lungs). Sometimes levomycetin is administered rectally.

The drug bioavailability in gastrointestinal tract is more than 90 %. Parenteral administration of levomycetin is used in treatment of meningitis. The degree of drug binding to plasma proteins is 50–60 %. Chloramphenicol easily penetrates into different tissues and fluids of the body. Nearly 90 % of administered chloramphenicol dose are metabolized in the liver. Unchanged 10 % of the drug is excreted through the kidneys that provides the antibacterial effect in the urinary tract.

Levomycetin is used only in treatment for severe infections caused by sensitive to levomycetin bacteria. Therapeutic indications for levomycetin are brain abscess, systemic salmonolesis, dysentery, richettsiosis, intrzoccular infections (eye burns, trachoma), brucellosis, tularemia, reactive arthritis, meningitis caused by *Haemophilus influenzae*, meningococci, and pneumococci. Aerosol thiamphenicol glycinate asetylcysteinate (co-formulated levomycetin preparation) is used in treatment of respiratory tract infections.

Chloramphenicol for oral intake is prescribed at 0.25–0.5 g dose given 4 times a day. A 20 % solution of levomycetin succinate is administered parenterally 2–3 times a day. Levomycetin liniment 10 %, or synthomycin liniment 10 %, is used in treatment of skin infections, burns, fissures, etc. Levomycetin is a component of different ointments (“*Levomekol*”, “*Levosin*”) and aerosols (“*Levovinisol*”, “*Olasol*”).

An accurate calculation of the dosage is based on the body weight of the patient in cases of enteral and parenteral administration of chloramphenicol. Course of treatment should not exceed 10–14 days. Control of the blood and liver function is required.

Levomycetin is a toxic antibiotic with narrow therapeutic action. The drug inhibits haematopoiesis that results in anemia, leukopenia, and thrombocytopenia. Chloramphenicol can cause acute drug-induced hemolysis in patients with genetically determined deficiency

of glucose-6-phosphate dehydrogenase. Non-hemolytic anemia can develop in patients with genetically determined deficiency of uridine-diphosphoglucuronic transferase. Levomycetin blocks mitochondrial ferrochelatase (enzyme which provides the iron inclusion in the structure of heme) that results in iron deficiency anemia, myodystrophy, and hypotrophy.

Gray baby syndrome is one of the possible complications caused by levomycetin in newborn infants and badies under 3 months. The gray baby syndrome is manifested by respiratory disturbances, severe metabolic acidosis, and vascular collapse. This complication is caused by insufficiency of mitochondrial respiratory enzymes in myocardium, slow excretion of drug with urine, and insufficiency of hepatic enzymes.

Sometimes the complications caused by chemotherapeutic effect of levomycetin are possible: aggravation of disease due to massive degradation of bacterial cells and release of endotoxins, dysbiosis, candidiasis, superinfection caused by *Pseudomonas aeruginosa*, resistant strains of staphylococci, and *Proteus*.

Aminoglycosides

Aminoglycosides are antibiotics containing aminosugars in molecules. These antibiotics are grouped into 4 generations:

– 1st generation: *streptomycin, neomycin, kanamycin, monomycin*.

– 2nd generation: *gentamicin*.

– 3rd generation: *tobramycin, sisomicin, amikacin, netilmicin*.

– 4th generation: *isepamicin*.

Aminoglycosides irreversibly inhibit 30S subunits of ribosomes that results in incorrect reading of mRNA and incorporation of mistaken amino acids in the protein structure. Also, aminoglycosides affect the structure and function of bacterial cytoplasmic membrane. Aminoglycosides are bactericidal antibiotics.

Aminoglycosides are broad-spectrum antibiotics. These drugs are active against Gram-negative aerobic (*Escherichia coli*,

Pseudomonas aeruginosa, *Klebsiella*, *Shigella*, *Proteus*, and enterobacteria) and Gram-positive coccal flora (staphylococci, streptococci, and pneumococci). Besides, gentamycin is active against *Francisella tularensis*; streptomycin, amikacin, and kanamycin – against *Mycobacterium tuberculosis*; monomycin – against *Entamoeba histolytica*, *Leishmania*, and *Trichomonas*. Isepamicin, besides the above mentioned flora, is active against *Citrobacter*, *Acinetobacter*, *Morganella*, *Listeria*, and *Nocardia*.

The bacterial resistance to aminoglycosides develops quickly due to the ability of bacteria to synthesize the enzymes which destroy aminoglycosides. There are 15 known enzymes that destroy aminoglycosides of the 1st generation, 10 enzymes destroying 2nd generation drugs, and only 3 enzymes that destroy aminoglycosides of the 3rd and 4th generations.

The main routes for aminoglycoside administration are intramuscular and intravenous (bolus or drop-by-drop). Aminoglycosides have poor solubility in lipids and their degree of absorption in gastrointestinal tract is low. The degree of aminoglycoside binding to plasma proteins is 10–30 %. These drugs have low ability to penetrate inside of the cells. But aminoglycosides easily penetrate through placenta, accumulate in the inner ear and adrenal cortex. Aminoglycosides do not undergo metabolism in the body and are excreted unchanged.

Presently, clinical use of the 1st generation aminoglycosides is restricted due to bacterial resistance and high drug toxocity. Thus, streptomycin is used only in treatment of tuberculosis, tularemia, and plaque. Widely used in the past combination of streptomycin and benzylpenicillin, nowadays, is used only in treatment of enterococcal endocarditis, due to high toxicity. Monomycin is used only in treatment of skin leishmaniasis. Tablets of kanamycin and neomycin are used in treatment of gastrointestinal infections (enterocolitis and dysentery) and for sanitation of intestine before surgery. Also, both agents are used externaly in treatment of dermatitis and infectious inflammatory diseases of skin. Kanamycin sulfate for parenteral administration is used in treatment of tuberculosis.

Gentamicin is a broad-spectrum aminoglycoside antibiotic of the 2nd generation. The most important is its activity against *Pseudomonas aeruginosa*, *Proteus*, *Escherichia coli*, *Enterobacter*, *Klebsiella*, and number of other bacteria, including staphylococci, resistant to the 1st generation aminoglycosides and benzylpenicillin. Bacterial resistance to gentamicin develops slowly. Normally, gentamicin does not penetrate through the blood-brain barrier, but in patients with meningitis the permeability of the blood-brain barrier is increased. The therapeutic indications for gentamicin are sepsis, urogenital infections, pneumonia, bronchitis, infections of central nervous system (including meningitis), osteomyelitis, peritonitis, postsurgical infections, infected wounds and burns, etc. The drug is administered intramuscularly or intravenously 2–3 times a day. Also, gentamicin is used topically in treatment of skin and eye infections caused by sensitive flora.

Third generation aminoglycosides are characterizied by higher activity against *Pseudomonas aeruginosa*, different strains of *Proteus*, *Klebsiella*, and *Enterobacter*. Amikacin also is active against *Mycobacterium tuberculosis*. Secondary resistance of bacteria to gentamicin develops significantly slowly than to gentamicin.

Fourth generation aminoglycoside isepamicin has longer duration of action than previous drugs. Isepamicin is administered intramuscularly or intravenously once a day. Toxicity of isepamicin is low.

Aminoglycoside therapy may be accompannied by development of serious side effects and complications.

Ototoxicity. Aminoglycosides accumulate in the outer and inner hair cells within the organ of Corti that results in degenerative changes of hair cells. Sensitive nerve fibers of the inner ear also degenerate. In case of streptomycin and gentamicin therapy vestibular disfunction develops initially. Other aminoglycosides may cause the initial hearing loss.

Nephrotoxicity occurs due to aminoglycoside accumulation in proximal convoluted tubules and functional disturbances of many

enzymes that cause the development of interstitial nephritis, impaired concentration of urine, proteinuria, and leukocyturia.

Blockage of neuromuscular synapses is accompanied by weakness of diaphragm and other respiratory muscles that can cause respiratory paralysis.

Aminoglycosides inhibit the absorption of nutrients in gastrointestinal tract. Other possible side effects of aminoglycosides include allergic reactions, polyneuritis, and phlebitis in case of intravenous administration.

Polymyxins (Cyclic Polypeptides)

The group is represented by such drugs as *polymyxin M*, *polymyxin B*, and *polymyxin E*.

Polymyxins affect the functions of cytoplasmatic membranes of bacteria. Antibiotics interact with phospholipids of membranes that results in the increase of membrane permeability. Polymyxins have a bactericidal action.

Antibacterial spectrum of polymyxins is narrow and includes Gram-negative bacteria: *Escherichia coli*, *Shigella*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Vibrio cholerae*, and most strains of *Pseudomonas aeruginosa*.

Polymyxin M is taken orally or used topically. The degree of the drug absorption in the gastrointestinal tract is about 1–2 %, but in patients with intestinal infections drug absorption increases up to 10–15 %. This fact should be considered because polymyxins are drugs with narrow therapeutic margin.

Polymyxin B and *polymyxin E* are administered intramuscularly, intravenously, into body cavities, and in aerosols for inhalation. The drugs have low degree of binding to plasma proteins. Polymyxins penetrate through cell membranes and into pleural and peritoneal fluids poorly. Therefore, in relevant cases these drugs are administered directly into the foci of the infection or intrathecally. Only 2–4 % of administered dose undergoes biotransformation. About 90 % of the dose is excreted unchanged through the kidneys. Polymyxins are active in the urinary tract only in the acidic urine.

The drugs are prescribed to be taken 3–4 times a day. For newborn infants, polymyxins should be taken only once a day.

Therapeutic indications for polymyxins are infections of intestine and urinary tract, pneumonia, endocarditis, and sepsis caused by sensitive flora. Also, polymyxins are used in treatment of purulent wounds, burns, purulent otitis and conjunctivitis, etc.

Polymyxins have the marked neurotoxicity and nephrotoxicity. These drugs can affect neuromuscular transmission (muscular weakness, and respiratory disturbances), vision, speech, and hearing. Therapy with polymyxins may be accompanied by drowsiness and irritability. Proteins, cylinders, and erythrocytes in the urine are manifestations of polymyxin nephrotoxicity.

Daptomycin is a new antibiotic with chemical structure similar to polymyxins. Daptomycin is a semisynthetic antibiotic active against Gram-positive and Gram-negative bacteria. Therapeutic indications for daptomycin include complicated infections of the skin and soft tissues and bacteremia caused by *Staphylococcus aureus* (including endocarditis). The drug is used only in the treatment of adults. The drug is administered intravenously once daily. Side effects are nausea, vomiting, muscular pain, etc.

Rifamycins

Rifamycin group includes such drugs as *rifamycin* (natural antibiotic) and *rifampicin* (semisynthetic antibiotic).

Rifamycins block the synthesis of RNA due to inhibition of DNA-dependent RNA-polymerase. Antibacterial effect of rifamycins is bacteriostatic. Spectrum of activity includes mainly Gram-positive bacteria: *Mycobacterium tuberculosis*, staphylococci, streptococci, pneumococci, meningococci, enterococci, gonococci, *Haemophilus influenzae*, *Mycobacterium leprae*, *Bacillus anthrax*, etc. Large doses of rifamycins affect also Gram-negative bacteria: *Escherichia coli*, *Shigella*, *Salmonella*, *Rickettsia*, *Klebsiella*, *Chlamydia*, *Brucella*, some strains of *Pseudomonas aeruginosa* and *Proteus*, etc. The bacterial resistance to rifamycins develops readily (in few days after the start of treatment).

Rifampicin is taken orally or administered intramuscularly or intravenously. The drug is easily absorbed in gastrointestinal tract. Rifampicin penetrates through tissue barrier, creates high concentrations in lungs, pleural cavity, peritoneal exudate, liquor, and bones. About 70 % of administered dose is metabolized in the liver. A part of rifampicin dose is excreted with bile into intestine where it is absorbed in the blood. About 30 % of the dose is excreted with the urine unchanged.

Rifampicin is mainly used to treat tuberculosis. Besides, the drug is prescribed to treat leprae, pneumonia, osteomielitis, urinary and biliary tract infections, acute gonorrhea, etc. The drug is also used to prevent rabies encephalitis in humans and meningitis in the carriers of meningococcal infection.

Rifampicin is a low-toxic antibiotic. Side effects of rifampicin include hepatotoxicity, leukopenia, thrombocytopenia, allergic reactions, and dispepsia. It is necessary to notice, that rifampicin turns the saliva, urine, sweat, feces, and tears an orange-red color. Rifampicin is not recommended for intake during first three months of pregnancy.

Lincosamides

The group includes such antibiotics as *lincomycin* and *clindamycin*.

Lincosamides inhibit the protein synthesis on the level of 50S subunit of bacterial ribosome. Lincosamides exhibit the bacteriostatic effect.

Antibacterial spectrum of lincosamides is broad, but preferably directed against Gram-positive bacteria: staphylococci, streptococci, pneumococci, *Corynebacterium diphtheriae*, and anaerobes (bacteroides, *Clostridium*, *Fusobacterium*). The activity of lincosamides against Gram-negative bacteria is less expressed. The following Gram-negative bacteria are sensitive to lincosamides: meningococci, gonococci, some strains of *Haemophilus influenzae*, and *Mycoplasma*. Clindamycin is also active against *Toxoplasma*

gondii, *Plasmodium*, and some strains of *Pneumocystis*. Clindamycin is 50 times more active against bacteroides than lincomycin.

Secondary bacterial resistance to lincosamides develops slowly.

Lincosamides are taken orally or administered intramuscularly and intravenously. Bioavailability of the drugs is 50 %. The degree of binding to plasma proteins is about 50 %. Lincosamides easily penetrate into different tissues and fluids of the body, except cerebrospinal fluid. Also, lincosamides are known to accumulate in bones. Nearly 80–90 % of administered dose is excreted in inactivated form with bile. Only 10–20 % of dose is excreted in unchanged form through the kidneys. Lincosamides exhibit the highest activity in alkaline environment. The drugs are prescribed to be taken 3–4 times a day.

Lincosamides are reserve antibiotics. The therapeutic indications for lincosamides are sepsis, endocariditis, artritis, osteomyelitis, lower respiratory tract infections, otitis, infected wounds, diabetic foot, toxoplasmosis, and tropical malaria. These drugs are also used to prevent infections after surgery in abdomynal cavity and on the pelvic organs.

Side effects of lincosamides are nausea, vomiting, abdominal pain, allergic reactions, leukopenia, and thrombocytopenia. Fast intravenous administration of the drugs can cause a decrease in blood pressure, dizziness, and a decrease in skeletal muscle tone. Lincosamides are contraindicated during pregnancy and in patients with severe hepatic and renal diseases.

Glycopeptides

The main representatives of this group are *vancomycin* and *teicoplanin (Targocid).*

Glycopetides inhibit the synthesis of bacterial cell wall and simultaneously affect the function of bacterial cytoplasmatic membrane. Glycopeptides are antibiotics with bactericidal activity.

Antibacterial spectrum includes Staphylococcus (including strains with resistance to other antibiotics), Streptococcus, Enterococcus, *Clostridium difficile*, and some other microorganisms.

Vancomycin is used in treatment of infections caused by Gram-positive bacteria: sepsis, endocarditis, meningitis, osteomyelitis, pneumonia, and enterocolitis (including pseudomembranous colitis). The drug is administered intravenously drop-by-drop 3–4 times a day.

Vancomycin is an antibiotic with high nephro- and ototoxicity. The fast drug administration can cause a massive release of histamine from basophils that results in low blood pressure and skin rashes. Vancomycin can cause phlebitis, neutropenia, and thrombocytopenia.

Teicoplanin has similar antibacterial spectrum with vancomycin. The drug is used in treatment of serious infections caused by sensitive bacterial flora (severe infections of respiratory and urinary systems, sepsis, peritonitis, etc.). Teicoplanin is administered intramuscularly or intravenously once a day.

Table 16 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Benzylpenicillinum-natrium	Intramuscularly 250 000–1 000 000 IU 4–6 times a day; intravenously slowly 1 000 000–2 000 000 IU; intravenously drop-by-drop 2 000 000–5 000 000 IU	Vials 250 000; 500 000 or 1 000 000 IU, powder for injection
Benzylpenicillinum-kalium	Intramuscularly 250 000–500 000 IU 4–6 times a day	Vials 250 000; 500 000 or 1 000 000 IU, powder for injection
Benzylpenicillinum-novocainum	Intramuscularly 300 000–600 000IU 2–3 times a day	Vials 300,000 or 600,000 IU, powder for injection
Bicillinum-5	Intramuscularly 1 500 000 IU once a month	Vials 1 500 000 IU, powder for injection
Oxacillinum-natrium	Orally, intramuscularly or intravenously 0.25–0.5 g 4–6 times a day	Tablets 0.25 or 0.5 g; capsules 0.25 g; vials 0.25 or 0.5 g of powder for parenteral administration

Continuation of the table 16

Drug name (Latin)	Single dose and route of administration	Drug product
Ampicillinum	Orally 0.5 g 3–6 times a day	Capsules and tablets 0.25 g
Amoxicillinum	Orally 0.25–1.0 g 3 times a day; intramuscularly or intravenously 1.0 g 2 times a day	Coated tablets 1.0 g; capsules 0.25 or 0.5 g; vials 1.0 g of powder for injection
Cefalexinum	Orally 0.25–0.5 g 4 times a day	Capsules 0.25 g; tablets 0.5 g
Cefotaximum	Intramuscularly or intravenously 0.5–1.0 g 2–3 times a day	Vials 0.5, 1.0 or 2.0 g of powder for injection
Cefoxitinum	Intramuscularly or intravenously 1–2 g 2–4 times a day	Vials 1.0 or 2.0 g of powder for injection
Ceftriaxone	Intramuscularly or intravenously 1–2 g once a day or 0.5–1.0 g twice a day	Vials 0.5, 1.0 or 2.0 g of powder for injection
Erythromycinum	Orally 0.1–0.25 g 4–6 times a day; into the lower eyelid pocket 1 % ointment up to 6 times a day	Tablets 0.1 or 0.25 g; 1 % ophthalmic ointment 7 g
Azithromycinum	Orally 0.25–1.0 g once a day	Capsules 0.125 or 0.25 g; tablets 0.5 g
Tetracyclinum	Orally 0.2–0.25 g 4 times a day; into the lower eyelid pocket 1 % ointment ointment 2–6 times daily	Coated tablets 0.05, 0.1 or 0.25 g; 1 % ophthalmic ointment 3.0 or 10.0 g
Methacyclini hydrochloridum	Orally 0.3 g 2 times a day	Capsules 0.15 or 0.3 g
Doxycyclinum	Orally 0.1 g 1–2 times a day or 0.2 g once a day	Capsules 0.1 g
Streptomycini sulfas	Intramuscularly 0.5 g 2 times a day	Vials 0.25, 0.5 or 1.0 g of powder for injection
Synthomycinum	1–10 % topically	1 %, 5 % or 10 % liniment

Continuation of the table 16

Drug name (Latin)	Single dose and route of administration	Drug product
Laevomycetinum	Orally 0.25–0.5 g 3–4 times a day; 1–2 drops of 0.25 % solution into the eye	Tablets 0.25 or 0.5 g; capsules 0.1, 0.25 or 0.5 g; vials 10 ml of 0.25 % solution
Gentamycini sulfas	Intramuscularly or intravenously 0.0004–0.001 g/kg 2–3 times daily; 1–2 drops of 0.3 % solution into the affected eye(s)	Ampoules 1 or 2 ml of 4 % solution; vials 0.08 g of powder for injection (for parenteral administration, it should be dissolved before using); ophthalmic solution: 0.3 % – 10 ml
Amikacini sulfas	Intramuscularly or intravenously (slowly or drop-by-drop) 0.007 5 g/kg twice a day or 0.005 g/kg 3 times a day	Vials 0.25, 0.5 or 1 g of powder for injection; ampoules 2 ml of 5 % or 25 % solution
Polymyxini M sulfas	Orally 500 000 IU 3–4 times daily; topically, in liniment (10 000 IU/1 g) or in solution (10 000–20 000 IU/ml) to treat wounds	Tablets 500 000 IU; vials 500 000 or 1 000 000 IU of powder (to prepare solution for external use); liniment 30,0 g (10 000 IU in 1 g)

Step 1. Tasks for Self-Control
Antibiotics

1. A 19-year-old patient has primary syphilis. He gets a complex therapy. Benzylpenicillin sodium is a part of this therapy. What is the mechanism of this drug action?

A. Blockade of DNA synthesis.

B. Blockade of cytoplasm proteins synthesis.

C. Blockade of microbe membrane peptidoglycan synthesis.

D. Blockade of RNA synthesis.

E. Blockade of thiol enzyme groups.

2. A 27-year-old woman has dropped penicillin containing eye drops. In few minutes there appeared feeling of itching, burning of skin, lips and eyelids edema, whistling cough, decreasing of blood pressure. What antibodies take part in the development of this allergic reaction?

A. IgE and IgG.

B. IgG and IgD.

C. IgM and IgD.

D. IgM and IgG.

E. IgA and IgM.

3. A patient was admitted to the infection unit with diagnosis of bacterial dysentery. On laboratory examinations it was revealed that causative element is sensitive to many antimicrobial medicines, but patient has anaemia. What drug is contraindicated to the patient?

A. Furazolidone.

B. Enteroseptol.

C. Ampicillin.

D. Levomycetin.

E. Phthalazolum.

4. A patient was admitted to the infection unit with diagnosis of bacterial dysentery. On laboratory studies it was revealed that causative element is sensitive to many antimicrobial medicines, but patient had anaemia. What medicine was contraindicated to the patient?

A. Phthalazolum.

B. Enteroseptol.

C. Furazolidone.

D. Ampicillin.

E. Levomycetinum (chloramphenicol).

5. A patient with pneumonia was treated with antibiotics for a long period. After treatment patient complains of frequent and watery stool, abdominal pain. What is the reason of intestine function disorder?

A. Bacteria toxins influence.

B. Antibiotic toxic influence on the GIT.

C. Intestinal disbacteriosis development.

D. Autoimmune reaction development.

E. Hereditary enzyme defect.

6. A 60-year-old patient was admitted to the surgical department because of infection caused by blue pus bacillus (Pseudomonas aeruginosa) which is sensitive to penicillin antibiotics. Indicate which of the given penicillins has marked activity to the Pseudomonas aeruginoca?

A. Methacillin.

B. Benzylpenicillin.

C. Phenoxymethylpenicillin.

D. Oxacillin.

E. Carbenicillin disodium.

7. A 50-year-old patient with typhoid fever was treated with levomycetin. The next day his condition became worse, temperature raised to 39.6^{0} C. What caused the worsening?

A. Allergic reaction.

B. The effect of endotoxin agent.

C. Irresponsiveness of an agent to the levomycetin.

D. Reinfection.

E. Secondary infection addition.

8. Penicillin-induced epilepsy has developed in a 28-year-old patient in the result of antibiotic therapy. What drug can cause this complication?

A. Isoniazid.

B. Doxycycline.

C. Rifampicin.

D. Benzylpenicillin sodium.

E. Amoxicillin.

9. Serious generalized septic infection menacing to life has developed in patient. What of the listed groups of chemotherapeutic agents should be used in this case?

A. Macrolides.

B. Tetracyclines.

C. Cephalosporins.

D. Laevomycetin.

E. Sulfonamides.

10. Treatment course of bacterial pneumonia included benzylpenicillin sodium salt. What is the mechanism of its antimicrobial action?

A. Inhibition of the cholinesterase activity.

B. Antagonism with the para-aminobenzoic acid.

C. Inhibition of the intracellular protein synthesis.

D. Inhibition of the microorganisms enzymes SH groups.

E. Inhibition of cell wall synthesis of the microorganism.

11. A patient suffering from stomach ulcer has been treated with antacid drug almagel. For acute bronchitis treatment he was prescribed antibiotic methacicline. However, within the next 5 days the fever didn't fall, cough and sputum nature remained unchanged. A physician came to the conclusion that the drugs were incompatible. What type of drug incompatibility is the case?

A. Direct antagonism.

B. Pharmaceutic.

C. Pharmacokinetic, biotransformation stage.

D. Pharmacokinetic, absorption stage.

E. Pharmacodynamic.

12. As a result of durative antibiotic therapy a 37-year-old patient developed intestinal dysbacteriosis. What type of drugs should be used in order to normalize intestinal microflora?

A. Vitamins.

B. Sulfanilamides.

C. Bacteriophages.

D. Eubiotics.

E. Autovaccines.

13. A doctor prescribed cephalosporin antibiotic to the patient after appendectomy for infection prevention. Antimicrobial activity of this group of antibiotics is based upon the disturbance of the following process:

A. Cholinesterase block.

B. Ribosome protein synthesis.

C. Energy metabolism.

D. Nucleic acid synthesis.

E. Microbial wall formation.

SULFONAMIDES

Sulfonamides are synthetic chemotherapeutic drugs – derivatives of sulfanilic acid.

Sulfonamides are classified as follows.

1. Resorptive sulfonamides.

1.1. Short-acting drugs: *streptocid, norsulfazol, etazol, sulfadiazine,* and *sulfadimezine*.

1.2. Intermediate-acting drugs: *sulfamethoxazole* and *sulfazine*.

1.3. Long-acting drugs: *sulfapyridazine* and *sulfadimethoxine*.

1.4. Ultra-long-acting drugs: *sulfalen* and *sulfadoxine*.

2. Sulfonamides acting in the intestinal lumen:

– *phthalazolum (phthalylsulfathiazole), phthazinum (phthalylsulfapyridazine),* and *sulginum (sulfaguanidine)*;

– co-formulated drugs of sulfonamides and 5-aminosalicylic acid: *salazodimethoxine* and *salazopyridazine (mesalazine).*

3. Sulfonamides for topical application: *sulfacyl sodium* and *silver sulfadiazine*.

Chemical structure of sulfonamides is similar to the structure of para-aminobenzoic acid (PABA). PABA is a component of folic acid. Folic acid participates in synthesis of nucleic acids and proteins

(transfers the one-carbon radicals). A significant number of bacteria synthesize folic acid. Due to structural resemblance, sulfonamides are competitive antagonists of PABA. When concentration of sulfonamides in environment is higher than PABA concentration, bacterial cells absorb molecules of sulfonamides instead of molecules of PABA. Also, sulfonamides are competitive inhibitors of dihydropteroate synthase – a bacterial enzyme involved in folate synthesis. As a result, the synthesis of folic acid is violated with the following inhibition of protein and nucleic acid synthesis. Sulfonamides are bacteriostatic agents.

It is necessary to notice that human cells do not synthesize folic acid but require its dietary intake in the form of vitamin B_c, therefore, sulfonamides are not antimetabolites for human organism.

Sulfonamides have the broad spectrum of antibacterial action. These drugs are active against both Gram-positive and Gram-negative cocci (staphylococci, streptococci, pneumococci, meningococci, gonococci), as well as against *Haemophilus influenza, Bacillus anthracis, Yersinia pestis*, Brucella, *Vibrio cholerae*, *Corinebacterium diphtheriae*, *Shigella*, *Chlamidya*, *Toxoplasma*, *Plasmodium*, *Pneumocystis*, Actinomycetes, etc.

Resorptive sulfonamides are readily absorbed in gastrointestinal tract. The degree of plasma protein binding ranges from 20 % up to 90 %. The main step of drug metabolism, acetylation, take place in the liver. Acetylated forms have a higher ability to bind to plasma proteins and a low ability to penetrate into tissues. Acetylated sulfonamides do not have antibacterial properties. These metabolites are excreted through the kidneys without the following reabsorption.

Acetylated forms are badly dissolved in water and can form precipitate in the acid urine with the obstruction of renal tubules. This complication may be prevented by intake of sodium hydrocarbonate or alkaline mineral water (alkalinization of urine).

Sulfonamides easily penetrate through the blood-brain barrier. Significant drug concentrations are observed in kidneys, lungs, liver, skin, peritoneal and pleural fluids, milk, saliva, bile, urine, etc. Sulfonamides do not accumulate in the bones.

Long-acting and ultra-long-acting sulfonamides are slowly inactivated in organism. These drugs undergo a significant reabsorption in distal convoluted tubules. Therefore, these drugs have long duration of action.

Short-acting sulfonamides are prescribed to be taken 4–6 times a day in a daily dose 4–6 g. Intermediate-acting drugs are prescribed for 2 times a day intake in a daily dose 1–3 g. Short-acting and intermediate-acting sulfonamides are used to treat acute infections. Long-acting sulfonamides are prescribed to take once a day for treatment of chronic infections. Ultra-long-acting drugs are prescribed to be taken by the scheme (as a rule once a week).

Therapeutic indications for sulfonamides are infections of urinary, respiratory or biliary tracts, intestinal infections, infections of skin and soft tissues, etc.

Sulfonamides acting in intestinal lumen are prescribed for 4 times a day intake in a daily dose 4–6 g.

Co-formulated sulfonamides with 5-aminosalicylic acid are called salazosulfonamides. *Salazopyridazine* (*mesalazine*) is the most commonly used among them. Under the influence of bacterial enzymes in large intestine, salazosulfonamides are decomposed to sulfonamide and 5-aminosalicylic acid that provides the anti-inflammatory effect. Salazosulfonamides are used to treat nonspecific ulcerative colitis and Crohn's disease.

Sulfonamides for topical application are used in solutions, eye drops, ointments, pastes, antiseptic powders, or aerosols. Before drug application, skin breaks, wounds, or burns should be cleaned from the pus because it reduces sulfonamide activity owing to presence of PABA. Eye drops of sodium sulfacyl are used in treatment of blepharitis, corneal ulcers, and blennophthalmia.

Sulfonamides seldom cause the development of side effects. As a rule, undesirable phenomena develop due to overdose and include the following symptoms: central nervous system intoxication (dizziness, headache, depression of consciousness, nausea, and vomiting), hemolytic or aplastic anemia, granulocytopenia, thrombocytopenia, allergic reactions (dermatitis and skin rashes), and

nephrotoxicity (proteinuria, erythrocytes and drug microcrystals in urine, and low back pain). The formation of microcrystals may be prevented by intake of alkaline liquids, because in alkaline environment the ability of sulfonamides and their acetylated metabolites to precipitate is low. Sulfonamides should be prescribed with caution for patients with diseases of liver and kidney.

Sulfonamide and Trimethoprim Co-Formulations

There is a number of drug co-formulations comprising sulfonamides and trimethoprim: *Co-trimoxazole (Biseptol, Bactrim, Groseptol), Sulfaton, Lidaprim, Poteseptil,* etc. The optimal ratio of trimethoprim to sulfonamide is 1:5. Thus, the most commonly used drug Biseptol contains 400 mg of *sulfamethoxazole* and 80 mg of *trimethoprim*.

A combination of sulfonamides with trimethoprim provides the possibility to block the synthesis of tetrahydrofolic acid in two steps:

– sulfonamide compete with PABA;

– trimethoprim blocks the enzyme, providing transformation of dihydrofolic acid into tetrahydrofolic acid – dihydrofolate reductase.

Due to this mechanism, co-formulated drugs have bactericidal effect. The bacterial resistance to combination drugs develops slowly.

It is necessary to notice that human dihydrofolate reductase is 50 000 times less sensitive to trimethoprim than bacterial enzyme.

Trimethoprim is readily absorbed in gastrointestinal tract and easily penetrates into tissues and fluids of the body. Nearly 50–60 % of the administered dose is exscreted from the body with urine. The rest is excreted with bile, sputum, etc.

Biseptol is used to treat infections of moderate severity. Children older than 12 eyars and adult patients should take 2 tablets of Biseptol twice a day. There are Bactrim or Septrin solutions in ampoules for intravenous infusion. The content of the ampule should be diluted with 5 % dextrose in water and administered intravenously drop-by-drop.

Therapeutic indications for Biseptol are as follows: respiratory tract infections (acute bronchitis, pneumonia, icluding pneumonia caused by Pneumocystes), urinary tract infections, enteritis, colitis, otitis, meningitis, sepsis, toxoplasmosis, and tropical malaria.

Side effects of co-formulated drugs are allergic reactions, nephrotoxicity, hepatotoxicity, methemoglobinemia, hemolytic anemia, neuritis, teratogenicity, porphyria (in patients with hereditary metabolic disorders), superinfection, deficiency of folic acid that results in anemia, hypotrophy, dyspepsia, and disturbances in spermatogenesis.

Co-formulated drugs are contraindicated to children under 6 years of age, pregnant women, patients with disturbances in haematopoiesis, and in diseases of liver and kidneys.

SYNTHETIC ANTIBACTERIAL DRUGS WITH DIFFERENT CHEMICAL STRUCTURE

This group includes antimicrobial drugs with different chemical structure which are classified into different groups.

1. Quinolone derivatives.
2. Nitrofuran derivatives.
3. Quinoxaline derivatives.
4. Oxazolidinones.

Quinolones

There are three generations of quinolones which differ by their antibacterial spectrum, activity, and toxicity.

First Generation Quinolones

First generation quinolones are *nitroxolinum, intestopan, chiniofonum, enteroseptol,* and *chlorchinaldolum*. There are combination drugs containing enteroseptol: *Mexaform* (contains *enteroseptol, entobex,* and *oxyphenonium bromide*) and *Mexasa* (*enteroseptol, entobex, bile acids, pancreatin,* and

bromelain). Oxyphenonium bromide is a drug with antispasmodic activity. Bromelain is a proteolytic enzyme contained in a pineapple.

First generation quinolones affect the activity of metal-containing bacterial enzymes and inhibit the synthesis of bacterial DNA. Besides, molecules of these drugs contain the atoms of I, Cl, or Br and cause the denaturation of bacterial proteins. Pharmacological effect of the 1st generation quinolones is bactericidal.

Antibacterial spectrum of the 1st generation drugs is broad and includes Gram-positive and Gram-negative bacteria, protozoa (amoeba, lamblia), and *Candida*. One should have in view that microorganisms become resistant to the 1st generation quinolones very quickly.

All drugs (except nitroxoline) are almost not absorbed from gastrointestinal tract, therefore they act only on microflora of the gastrointestinal tract. Most 1st generation drugs are taken orally 4 times a day.

About 50 % of orally taken *nitroxoline* is absorbed in the blood. Nitroxoline binds to plasma proteins, poorly penetrates into fluids and tissues of the body (except renal tissue and prostate), and is excreted through the kidneys unchanged. Nitroxoline is used in treatment for urinary tract infections. The toxicity of nitroxoline is low. Side effects are allergic reactions and dispeptic disorders. The drug turns the urine violent yellow.

Chiniofonum is used mainly to treat amoebic dysentery. *Intestopan*, *enteroseptol*, and *chlorchinaldolum* are used to treat intestinal infections (dysentery, salmonellosis, intestinal disorders caused by staphylococci, Proteus, enterobacteria, etc.). *Mexaform* is a drug of choice in case a patient is concerned about painful spasms of intestinal smooth muscles. In case of meteorism, *Mexasa* is preferable. Iodine-containing drugs are contraindicated to patients with hyperthyreosis.

Second Generation Quinolones

Second generation quinolones are *nalidixic acid, oxolinic acid (gramurin),* and *pipemidic acid (palin)*. These drugs inhibit metal-containing enzymes of bacterial cells. Depending on concentration, the 2nd generation quinolones cause bacteriostatic or bactericidal effect.

Antibacterial spectrum of the 2nd generation quinolones directs upon Gram-negative bacteria (*Escherichia*, *Shigella*, *Salmonella*, *Klebsiella*, and *Proteus*). *Pseudomonas aeruginosa* is resistant to the 2nd generation drugs. Bacteria quickly develop secondary resistance to these drugs.

The 2nd generation quinolones are prodrugs, which after hydroxylation in liver, are transformed into pharmacologically active substances.

The drugs are taken orally because they have high bioavailability in the gastrointestinal tract. The 2nd generation drugs poorly penetrate into tissues and fluids of the body, being excreted through the kidneys. These drugs are prescribed to be taken 4 times a day. Therapeutic indications for the 2nd generation quinolones are acute and chronic infections of urinary tract. It is necessary to acidify the urine during treatment with these drugs.

Side effects of the 2nd generation quinolones are allergic reactions, dyspetic disorders, headache, photodermatosis, and isomnia. The drugs are contraindicated to patients with severe violations of hepatic and renal functions, for pregnant women in first 3 months of pregnancy, and for children under 2 years of age.

Third Generation Quinolones (Fluoroquinolones or Systemic Quinolones)

Molecules of these drugs contain fluorine and piperidine radicals that significantly influence upon their antibacterial spectrum and pharmacological properties. Fluoroquinolones are classified into the following groups:

– monofluoroquinolones: *norfloxacin (floxacin), pefloxacin (abactal), enoxacin, ofloxacin (tarivid), ciprofloxacin (ciprobay), pufloxacin*;

– difluoroquinolones: *sparfloxacin (zagam), lomefloxacin (maxacvin)*;

– trifluoroquinolones: *tosufloxacin, fleroxacin (Quinodis).*

Fluoroquinolones inhibit DNA gyrase (also known as topoisomerase II) activity – an enzyme essential for bacteria viability. DNA gyrase paticipates in the process of DNA replication. DNA gyrase provides the formation of negative supercoiling in the relaxed circular prokaryotic DNA molecules. Interaction between gyrase and DNA leads to DNA winding around the enzyme. There is a positive supercoiling in places of DNA which is associated with gyrase. Thereafter, the enzyme makes a double-stranded break in DNA, moves a double strand from inside to outside, and stitches segments back together. Thus, positive supercoiling of DNA transformes into negative supercoiling that promotes the movement of DNA polymerase along DNA.

Bacterial DNA gyrase essentially differs from human DNA gyrase. This provides the high selectivity of fluoroquinolones against microorganisms and their low toxicity for humans.

Some fluoroquinolones (ofloxacin, ciprofloxacin, and lomefloxacin) have an ability to inhibit the enzyme that provides the synthesis of the SOS-system proteins. These proteins protect the bacterial cell from unfavorable external factors and are responsible for changes of the rod-shaped bacteria (filamentous forms) before cell division. Fluoroquinolones are bactericidal agents.

Fluoroquinolones are ultra-broad-spectrum antibacterial agents. Gram-negative microflora is more sensitive than Gram-positive

bacteria to these drugs. Fluoroquinolones are active against gonococci, *Escherichia coli*, *Shigella*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Mycoplasma*, *Chlamidia*, etc. There are resistant bacteria to fluoroquinolones: Spirochaetales, fecal enterococci, and anaerobes. It is necessary to notice that sparfloxacin has the highest activity against Gram-positive cocci, *Chlamidia*, *Mycoplasma*, *M. tuberculosis* and *M. leprae*.

Moxifloxacin (Avelox, Avalox) exhibits the high activity against streptococci, staphylococci, *Chlamydia*, *Mycoplasma*, *Ureaplasma*, and anaerobes. In activity against anaerobes, moxifloxacin is similar to metronidazole and imipenem.

Bacteria slowly develop the secondary resistance to fluoroquinolones. As soon as bacterial resistance is developed, it spreads to the 1st and the 2nd generation quinolones and a significant amount of antibiotics (tetracyclines, chloramphenicol, and β-lactam antibiotics). Therefore, fluoroquinolones should be used only as reserve drugs.

There are known such new fluoroquinolones as *gatifloxacin*, *gemifloxacin*, and *levofloxacin*. The drugs have high activity against Gram-positive and Gram-negative bacteria, especially against pathogens causing respiratory tract infection and tuberculosis. These new agents are taken orally.

Fluoroquinolones are taken orally, administered intravenously, or used externally. For intravenous administration, the drug (e. g. ciprofloxacin, pefloxacin) is diluted ex tempore. Solutions should be protected from light.

Fluoroquinolones are readily absorbed in the gastrointestinal tract. Simultaneous intake of fluoroquinolones with antacids and iron-containing drugs should be avoided, because the bioavailability of fluoroquinolones is reduced. The degree of fluoroquinolone binding to plasma proteins is about 40 %. Fluoroquinolones readily penetrate into main tissues and fluids of the body, but only some drugs (ofloxacin, pefloxacin, and ciprofloxacin) can penetrate through the blood-brain barrier. The main route of drug elimination

is kidneys. Fluoroquinolones are prescribed to be taken 1–2 times a day.

Fluoroquinolones should be prescribed only in cases when broad-spectrum antibiotics are ineffective. The therapeutic indications for fluoroquinolones are infections of urinary tract (foremost caused by *Pseudomonas aeruginosa*), respiratory system, gastrointestinal tract, severe purulent surgical infections caused by multiresistant microflora or *Staphylococcus aureus*, treatment and prevention of infections in patients with neutropenia, oncological diseases, and immunodeficiency.

Fluoroquinolones are low-toxic drugs. Their side effects are dyspepsia, skin rash and other allergic reactions, headache, dizziness, insomnia, photosensitization, temporal arthralgia, disbiosis, and disturbances of renal and hepatic functions.

Nitrofurans

Nitrofurans include such drugs as *furacilinum (nitrofural, nitrofurazone), furazolidone, furaginum (furazidin), furadoninum (nitrofurantoin),* and *furazolinum.*

Nitrofurans form the complex compound with bacterial DNA, affect the transport of electrons in respiratory chain, violate the redox processes in citric acid cycle. It results in the disturbances of cytoplasmic membrane function and destruction of bacterial cell wall. Depending on a dose, nitrofurans exhibit bacteriostatic or bactericidal effect. Unlike other antibacterial drugs which inhibit immunity, nitrofurans slightly increase the resistance of macroorganisms to infection (nitrofurans stimulate phagocytosis, etc.). Under the nitrofuran influence, the production of toxins by bacteria is reduced. Nitrofurans keep their activity in precence of pus and other products of tissue disintegration.

Nitrofuran antibacterial spectrum is broad and includes such microorganisms as Gram-positive and Gram-negative bacteria (staphylococci, pneumococci, streptococci, *Klebsiella*, *Proteus*, *Enterobacter*, meningococci, gonococci, etc.) and protozoa (*Trichomonas* and *Giardia lamblia*).

The bacterial resistance to nitrofurans develops slowly and is not cross-reactive with sulfonamides and antibiotics.

Nitrofurans are taken orally after a meal. Furaginum is also used for intravenous administration. Furacilinum and furaginum are used topically. The degree of nitrofuran absorption in gastrointestinal tract is about 50 % (for furazolidone – only 30 %). The degree of binding with plasma proteins is very low. Nitrofurans readily penetrate into lymph and accumulate in the bile duct. Only 10 % of administered nitrofuran dose undergoes biotransformation. Nitrofurans are excreted from the body through the kidneys. The intensity of excretion is higher in alkaline urine. In acid urine, nitrofurans undergo reabsorption that provides for their accumulation. Nitrofurans are prescribed to be taken 4 times a day.

Furadoninum (nitrofurantoin) is mainly used in treatment of urinary tract infections (pyelonephritis, cystitis, and uretritis). Also, furadoninum is used to prevent infection in cystoscopy and prolonged catheterization.

Furazolidone is poorly absorbed in the gastrointestinal tract that allows it to be used in enterocolitis treatment. The drug is also used to treat lambliasis and colpitis caused by Trichomonas. Furazolidone is taken orally and applied intravaginally or rectally.

Furacilinum (nitrofural) is known as antiseptic for external use. The drug is used for antiseptic rinsing, washing of wounds, burns, and bedsores. Also, furacilin is used in form of eye and ear drops.

Side effects of nitrofurans are expressed by loss of appetite, nausea, epigastric pain, allergic reactions (skin rash, bronchospasm, fever, etc.), disturbances of renal function, neuritis, and methemoglobinemia. Drinking plenty of fluids and taking in H_2-receptor antagonists and vitamins of group B are prescribed when treating by nitrofurans to prevent or diminish their side effects.

Quinoxaline Derivatives

Quinoxaline derivatives are *quinoxidine* and *dioxidine*. Quinoxalines are synthetic agents with bactericidal effect. The mechanism of their action is poorly understood. Antibacterial spectrum includes *Proteus*, *Pseudomonas aeruginosa*, *Klebsiella*, *Escherichia coli*, *Shigella*, *Salmonella*, staphylococci, streptococci, *Clostridium*, and *Bacteroides*. Bacteria slowly develop secondary resistance to quinoxalines.

Quinoxidine is taken orally 3–4 times a day after a meal. The drug is readily absorbed in the gastrointestinal tract. Dioxidine is administered intravenously drop-by-drop (0.1–0.2 % sterile solutions) or administered in body cavities. Also, solutions or ointments with dioxidine are used topically. Quinoxaline derivatives are excreted through the kidneys unchanged.

Quinoxaline derivatives are used as reserve drugs in treatment of purulent inflammatory processes of different localization: purulent pleuritis, lung abscess, peritonitis, pyelonephritis, cholecystitis, and severe sepsis.

Quinoxalines are quite toxic drugs. Their side effects are expressed by dispepsia, dizziness, headache, allergic reactions, candidiasis, muscle twitching, carcinogenesis, teratogenicity, etc.

Oxazolidinones

The representative of this new antibacterial group is *linezolid (Zyvox)*. Linezolid affects the syntheisis of nucleic acids and protein synthesis on ribosomes. As a rule, linezolid exhibits bacteriostatic effect, but against Gram-positive cocci the drug can produce the bactericidal effect.

Antibacterial spectrum of linezolid is broad and includes such microorganisms as aerobic Gram-positive bacteria and cocci, some Gram-negative bacteria, Mycobacterium tuberculosis, and many anaerobes.

Linezolid is administered intravenously or taken orally 1–2 times a day. The drug is readily absorbed in the gastrointestinal tract. Its bioavailability is about 100 %. The degree of binding to

plasma proteins is about 30 %. Inactivated linezolid is excreted through the kidneys (30 %) and liver (70 %).

The therapeutic indications for linezolid are sepsis, endocarditis, pneumonia, infections of skin and soft tissues, and other severe infections caused by Gram-positive cocci.

The side effects of linezolid are dysbiosis, candidiasis, nausea, vomiting, headache, and changes in gustatory perception. The prolonged drug use can cause thrombocytopenia, peripheral neuropathy (including optic nerve), allergic reactions, pancreatitis, and liver damage.

Table 17 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Sulfadimezinum	Orally 1st administration – 2.0 g; all subsequent administrations 1.0 g 4–6 times daily	Tablets 0.25 or 0.5 g
Aethazolum	Orally 1.0 g 4–6 times daily	Tablets 0.25 or 0.5 g
Sulfacylum-natrium	Intravenously slowly 3–5 ml of 30 % solution twice a day; 1–2 drops into eyes 2–6 times daily	Ampoules 5 ml of 30 % solution; eye drops: bottles 10 ml of 20 % or 30 % solution
Sulfadimethoxinum	Orally 1st administration – 1.0–2.0 g; all subsequent administrations 0.5–1.0 g 1–2 times a day	Tablets 0.2 or 0.5 g
Phthalazolum	Orally 1.0 g 4–6 times daily	Tablets 0.5 g
Biseptol-480	Orally 2 tablets 2 times daily; intravenously drop-by-drop 10 ml deluted in 250 ml of isotonic solution of NaCl twice a day	Tablets containing 0.4 g of sulfamethoxazole and 0.08 g of trimethoprim; ampoules 5 ml
Nitroxolinum	Orally 0.1 g 4 times a day	Coated tablets 0.05 g
Acidum nalidixicum	Orally 0.5–1.0 g 4 times daily	Tablets or capsules 0.5 g

Continuation of the table 17

Drug name (Latin)	Single dose and route of administration	Drug product
Furazolidonum	Orally 0.1 g 4 times daily	Tablets 0.05 g
Ciprofloxacinum	Orally 0.25–0.75 g 2 times daily; intravenously drop-by-drop 0.2–0.4 g with 50 ml of isotonic sodium chloride solu-tion 2 times a day	Tablets 0.25; 0.5 or 0.75 g; ampoules 10 ml of 1 % solution

Step 1. Tasks for Self-Control
Sulfonamides. Synthetic Antimicrobial Drugs

1. Gonorrhoea was revealed in the patient on bacterioscopy of the smear from urethra. Taking into account that medicines for gonorrhea are fluorquinolones, patient should be prescribed:

A. Fluorouracil.

B. Ciprofloxacin.

C. Furasolidone.

D. Cefazolin.

E. Urosulfanum.

2. A patient with pneumonia has intolerance to antibiotics. Which of the combined sulfanilamide drug should be prescribed to this patient?

A. Biseptol.

B. Streptocid.

C. Aethazol.

D. Sulfadimethoxine.

E. Sulfacylum natrium.

3. Relative granulocytopenia is observed in patient after course of treatment with sulfonamides. It is known that patient has tendency to allergies. Point out an immunologic process which is the cause of granulocytopenia?

A. Increased activity of macrophages.

B. Decrease of immunologic tolerance.

C. Formation of immunologic complexes in blood.

D. Increased activity of killer lymphocytes.

E. The lysis of leucocytes which are acquired from antigenic properties.

4. Combined sulfonamide drug with bactericidal effect was prescribed to patient with pneumonia. Which drug was prescribed?

A. Phthalazolum (phthalylsulfathiazole).

B. Aethazolum (sulfaethidole).

C. Norsulfazol (sulfathiazole).

D. Bactrim.

E. Sulfalen.

5. A doctor prescribes biseptol to patient with tonsillitis. What is the priority of biseptol in comparison with other sulfonamides?

A. Biseptol has less degree of binding with plasma proteins.

B. Trimethoprim increases the imitation of PABA by sulfonamides.

C. Biseptol better penetrates into the microorganisms.

D. Trimethoprim decreases the sulfonamide biotransformation.

E. Trimethoprim blocks the next stage of folic acid metabolism.

6. A doctor prescribes sulfonamide to patient with pneumonia. What is the mechanism of sulfonamides action?

A. Increase of bacterial cell membrane permeability.

B. Competitive antagonism with para-aminobenzoic acid (PABA).

C. Regulation of vessels tone.

D. Influence upon bacterial cell wall.

E. Blockage of SH groups of bacterial enzymes.

7. A patient with bacterial dysentery receives phthalazolum. Why is this drug used only for treatment of intestinal infections?

A. Drug is easily eliminated from the body.

B. Drug has high degree of reabsorption in the kidneys.

C. Drug undergoes enterohepatic circulation.

D. Drug is easily absorbed in the blood.

E. Drug acts only on the intestine because it isn’t absorbed into the blood.

8. A patient received sulfalen for treatment of chronic infection. Haemolysis of erythrocytes develops in the patient in several days after initiation of treatment. Deficiency of which enzyme is the cause of this complication?

A. N-acetyltransferase.

B. Cholinesterase.

C. Acetaldehyde dehydrogenase.

D. Glucose-6-phosphate dehydrogenase.

E. MAO.

9. A 7-years-old child receives phthalazolum for treatment of enterocilitis. What is the mechanism of drug action?

A. Blockage of peptidyl transferase.

B. Inhibition of dihydropteroate synthase.

C. Inhibition of RNA-polymerase.

D. Inhibition of DNA-transcriptase.

E. Inhibition of DNA-polymerase.

10. A doctor prescribed sulfonamide for treatment of patient with infection of urinary tract. Which drug was prescribed by the doctor?

A. Sulfadimethoxine.

B. Phthalazolum.

C. Urosulfanum.

D. Sulfacylum-natrium.

E. Sulginum.

ANTISYPHYLITIC DRUGS

Antisyphylitic drugs are used to treat syphilis. The infectious agent causing syphilis is *Treponema pallidum*. The antisyphylitic therapy is complex and requires pill-dosing regimen.

Presently, three groups of drugs are most commonly used to treat syphilis: antibiotics, fluoroquinolones, and bismuth preparations.

Classification of antisyphylitic drugs is as follows.

1. Antibiotics:

– penicillins: *benzylpenicillin sodium, benzylpenicillin potassium, benzylpenicillin novocaine salt, bicillin-1, bicillin-5, ampicillin, oxacillin*;

– macrolides and azalides: *erythromycin, oleandomycin, azithromycin*;

– cephalosporins: *cefazolin, ceftriaxone*, etc;

– tetracyclines: *doxycycline, tetracycline*.

2. Fluoroquiniolones: *ofloxacin*, etc.

3. Bismuth-containing drugs: *biiochinol, bismoverol*.

Both short-acting and long-acting penicillins are used to treat syphilis. Penicillins are the most efficient drugs for syphilis therapy and are active against *Treponema pallidum* in all stages of the disease. Penicillins are especially effective if used in combination with bismuth preparations.

In case of individual intolerance to penicillins, other effective antibiotics (macrolides, tetracyclines, and cephalosporins) are prescribed for syphilis treatment. But all of them are less active against *Treponema pallidum*.

Bismuth-containing drugs are biiochinolum and bismoverolum. Both drugs are the suspensions of bismuth-containing substances in peach kernel oil. These drugs are active only against *Treponema pallidum*. Bismuth blocks the thiol enzymes of *Treponema*. The activity of bismuth-containing drugs is less than penicillin activity, and their effect develops slower. Bismuth-containing drugs are especially effective in neurosyphilis. Both drugs are non-absorbable in gastrointestinal tract, therefore they are administered intramuscularly. Bismuth-containing drugs accumulate in the body

with a significant accumulation in the bones, kidneys, liver, and nervous tissue. The routes of drug excretion are kidneys and intestine. Bismuth-containing drugs are used in treatment of all forms of syphilis.

The common complication of bismuth therapy is so-called "bismuth flu": generalized weakness, fever, and fatigue. These symptoms appear right after drug administration: gray colored border around the edge of the gums, dermatitis, gingivitis, colitis, stomatitis, and dark spots on the cheeks appear subsequently. Sometimes, leukopenia and disturbances of hepatic and renal functions are observed.

Iodine preparations are used in resorption of intracranial gummas in the tertiary stage of syphilis.

Table 18 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Benzylpenicillinum -natrium	Intramuscularly 250 000–1 000 000 IU 4–6 times daily	Vials 250 000; 500 000 or 1 000 000 IU of powder for injection
Bicillinum-5	Intramuscularly 1 500 000 IU 1 time per month	Vials 1 500 000 IU of powder for injection
Biiochinolum	Intramuscularly 2–3 ml 1 time per 3 days	Vials 100 ml
Bismoverolum	Intramuscularly 1.5 ml 2 times per week	Vials 100 ml

ANTITUBERCULOSIS DRUGS

Tuberculosis is an infective disease caused by three species of Mycobacterium: *M. tuberculosis*, *M. bolis* and *M. avium*. *M. tuberculosis* is a so-called "human" specie which is transmitted only from human to human. *M. bolis* and *M. avium* (bovine and avian species) can infect both humans and animals.

Modern tuberculosis is characterized by mainly bronchopulmonary localization (about 80 % of cases). According to WHO, there are about 20 million sick people with active tuberculosis around the world. Annually, from 50 to 100 million people are infected and more than 3 million people die. The risk of falling ill is significantly increased in people with immunodeficiency: AIDS/HIV patients, smokers, patients with chronic bronchopulmonary diseases, and in malnutrition. The stress is not the least among health risk factors. Thus, the incidence of tuberculosis is sharply increased in times of crises and wars.

Antituberculosis drugs include both antibiotics and synthetic agents. Synthetic drugs are active only against species of *Mycobacterium* causing tuberculosis. Some of them are also active against *Mycobacterium leprae*. Antibiotics which are used to treat tuberculosis are broad spectrum antibiotics mainly of rifamycin and aminoglycoside groups.

According to reccomendations of the International Union Against Tuberculosis and Lung Disease (1997), antituberculosis drugs are classified into the following groups based on their activity.

1. Most effective antituberculosis drugs.
   1.1. Isonicotinic acid derivatives: *isoniazid, ftivazide, saluzidum*.
   1.2. Rifamicins: *rifampicin, rifabutin, rifaximin*.
2. Drugs with high antituberculosis activity:
   2.1. Aminoglycosides: *streptomycin, kanamycin, amikacin*.
   2.2. Derivatives of isonicotinic acid: *pyrazinamide, ethionamide, prothionamide.*
   2.3. Aminobutanol derivatives: *ethambutol*.

2.4. Fluoroquinolones: *ofloxacin, sparfloxacin, lomefloxacin, ciprofloxacin*.

2.5. Antibiotics of different groups: *florimycin, cycloserine, capreomycin.*

3. Drugs with moderate antituberculosis activity:

3.1. Para-aminobenzoic acid derivatives: *sodium para-aminosalicylate (PAS)* and *calcium para-petrolyl-aminosalicylate (Bepascum)*.

3.2. Thiosemicarbazone derivatives: *thioacetazone*.

According to the degree and reliability of action upon *M. tuberculosis*, antituberculosis drugs are divided into two groups.

1. First-line drugs: *isoniazid, rifampicin, ethambutol, pyrazinamide,* and *streptomycin*.
2. Second-line drugs: *ethionamide, prothionamide, cycloserine, florimycin, capreomycin, amikacin, kanamycin, lomefloxacin, ofloxacin, ciprofloxacin,* and *PAS*.

There are several populations of *M. tuberculosis*. First population mycobacteria are located outside the cells, have intensive metabolism and rapidly grow in the acidic environment. This population is predominant in acute phase of disease. Dispite of high sensitivity of these bacteria to antituberculosis drugs, the resistant strains are often found between them. Therefore, the treatment of tuberculosis starts with the use of 3–5 drugs.

Second population mycobacteria are located inside the cells (mainly within macrophages) and characterized by low metabolic rate and slow growth in the acidic environment. This population is typical for chronic forms of tuberculosis. Second population mycobacteria are sensitive to pyrazinamide, isoniazid, and rifampicin. Aminoglycosides do not penetrate into the cells, therefore, they do not significantly affect this population.

Third-population mycobacteria are characterized by slow growth and location in caseous foci. This population is sensitive only to pyrazinamide and rifampicin. Second- and third population mycobacterium can transform into latent forms. In unfavourable

conditions (reduction of immunity, deterioration of the living conditions of the patient), these latent forms cause the disease recurrence. The latent forms of mycobacteria are sensitive to rifampicin and pyrazinamide.

There are some peculiarities of tuberculosis treatment. It is necessary to choose the drugs to which mycobacteria are sensitive. The course of treatment can take from several months to several years. Pharmacotherapy includes simultaneous intake of several drugs. A prolonged antituberculosis therapy is accompanied by the development of bacterial resistance and toxic effects in the human body. The combined pharmacotherapy with 3–5 antituberculosis drugs prevents the bacterial resistance. The efficacy of tuberculosis therapy increases if antituberculosis drugs are used together with immunomodulators. Also, ambenum is used because this drug prevents the lungs' fibrosis. In prolonged antituberculosis therapy, such agents as insulin (8 units a day), glucocorticoids, folic acid, and stimulator of phagocytosis flurenizid are used. Hepatoprotectors are prescribed to prevent liver damage (Essentiale, Solcoseryl, LIV 52, etc.).

From the clinical point of view, all tuberculosis patients are divided into 4 groups. The first group includes the patients who release mycobacteria into the external environment. The short-term therapeutic regimen (during 6 months) is used to treat such patients. The treatment is performed in two phases. A combination of four drugs is prescribed in the initial phase of treatment. This combination includes isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin. The duration of this phase is 2 months. The second phase lasts four months. Two drugs – isoniazid and rifampicin – are prescribed in this phase. As a result of therapy, the release of mycobacteria is terminated in 100 % of patients and closing of caverns is observed in 89 %.

The second group includes tuberculosis patients who do not release mycobacteria. These patients are treated by 4-drug combination (isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin) during four months.

The third group includes elderly patients. A so-called “mild” regimen of intermittent therapy is used in their treatment. According to this regimen, three drugs are prescribed to be taken two times a week during the first half-year.

The fourth group includes healthy people at high risk for tuberculosis: persons who contact sick people releasing mycobacteria, patients with hyperergic tuberculin reaction (more than 6 mm), healthcare workers of TB dispensary, etc. They take isoniazid once a day after a meal during 2–3 moonths or three times a week (intermittent method).

Most Effective Antituberculosis Drugs:

Isonicotinic Acid Derivatives

Hydrazides of isonicotinic acid include such drugs as *isoniazid, ftivazide, saluzidum, prothionamide,* and *ethionamide*.

Isoniazid is most commonly used among them. The drug exerts high activity against *Mycobacterium tuberculosis*. Isoniazid acts upon both extracellular and intracellular mycobacteria.

A mechanism of isoniazid action is not clear enough. The drug affects synthesis of mycolic acids which are essential for the cell wall of mycobacteria, because mycolic acids are structural components of the cell wall only for mycobacteria, therefore isoniazid action is highly specific, and it is active only against mycobacteria. Besides, there is a viewpoint that isoniazid also inhibits the nucleic acid synthesis. Effect of isoniazid is bactericidal.

Isoniazid is taken orally or administered intramuscularly, intravenoulsly, by inhalation, and into cavernas. Orally, isoniazid is taken 1–3 times a day after a meal. The drug is readily absorbed in the gastrointestinal tract. Isoniazid easily penetrates through tissue barriers including the blood-brain barrier.

The rate of isoniazid inactivation (hepatic acetylation) significantly differs in different patients. This fact should be taken into account for drug dosing. The speed of hepatic acetylation is genetically determined, and about 50 % of European population has a low speed of this reaction. In these patients (so-called “slow

acetylators"), plasma drug concentration reduces 2–2.5 times slower than in "fast acetylators". The main route of isoniazid excretion is kidneys.

Intramuscular or intravenous routes of isoniazid administration are used in severe forms of tuberculosis. After intravenous drug administration, a patient should lie at least during 1–1.5 hours. Usually, intravenous administration of isoniazid improves the pulmonary blood circulation.

Therapy with isoniazid is accompanied by significant side effects and complications. Neurotoxic effects are the first among them: neuritis, damage of ocular nerve, insomnia, psychic disturbances, dizziness, and memory loss. Nausea, vomiting, constipation, dry mouth, and allergic skin rash are possible due to the drug intake. Isoniazid affects the synthesis of vitamin B_6 active form – pyridoxal phosphate. The last one is the essential co-enzyme for deamination and transamination of amino acids and participates in protein synthesis. Therefore, isoniazid can cause disturbances of protein synthesis with the following muscular atrophy and anemia. Also, gynecomastia in males and menorrhagia in females are possible side effects of isoniazid. Pyridoxine, glutamic acid, thiamine, and ATP-Long are used for reduction of isoniazid toxicity.

Isoniazid contraindications are epilepsy and other convulsive diseases, disturbances of hepatic and renal functions, marked atherosclerosis, and phlebitis.

Other derivatives of isonicotinic acid (ftivazide, saluzid, ethionamide, prothionamide) are less active in comparison with isoniazid. These drugs are used in case of isoniazid intolerance.

Rifamicins

The main representative of this antibiotic group is *rifampicin.* This broad-spectrum antibiotic is active against *Mycobacteria,* Gram-positive and Gram-negative bacteria, including some strains of *Pseudomonas aeruginosa, Proteus,* and capsular bacteria.

Rifampicin inhibits the RNA synthesis due to blockage of DNA-dependent RNA-polymerase. Depending on the used dose,

antibacterial effect of rifampicin is either bacteriostatic or bactericidal. Bacterial resistance to rifampicin develops quickly.

Rifampicin is taken orally 1–2 times a day 0.5–1 hour before a meal. The drug is easily absorbed from gastrointestinal tract. Maximum blood concentration is achieved in 2–2.5 hours. Also, rifampicin is administered intravenously drop-by-drop (only for adults). Duration of the drug action is 8–12 hours. Rifampicin readily penetrates through the histohematic barrier and is excreted with bile, urine, and bronchial secret. The drug can turn urine, tears, saliva, and other body fluids red.

As a rule, rifampicin is prescribed together with other antituberculosis agents. Also, rifampicin is used as a reserve drug for treatment of other infectious diseases. Sometimes, rifampicin is used to treat lepra and rabies (in incubation period, because the drug inhibits the development of rabies encephalitis).

Rifampicin is hepatotoxic and immunosupressive agent. To prevent immunodeficiency, immunocorrectors (levamisole, Tactivin, etc.) are used during therapy with rifampicin.

Rifampicin therapy may be complicated by leukopenia, dyspepsia, and allergic reactions. The drug is contraindicated to pregnant women, infants, and in severe hepatic and renal diseases.

Drugs with High Antituberculosis Activity:

Aminoglycosides

Streptomycin is an antibiotic of broad antibacterial spectrum. The drug is active against mycobacteria and most Gram-positive and Gram-negative bacteria. Anaerobes, spirochetes, rickettsia, viruses, fungi, and protozoa are not sensitive to streptomycin.

Streptomycin inhibits the protein synthesis and affects the permeability of the bacterial cell membrane. Streptomycin is a bactericidal medication.

Streptomycin is badly absorbed in the gastrointestinal tract and therefore it is administered intramuscularly. Maximum blood concentration of streptomycin is achieved in 1–2 hours after administration. For tuberculosis treatment, the drug is administered

1–2 times a day. For treatment of other infections, streptomycin may be administered 3–4 times a day. Sometimes, streptomycin is administered intratrachealy (aerosol) or into cavernas (10 % solution, once a day, only in hospital). Streptomycin is excreted unchanged through the kidneys.

Ototoxic effect of streptomycin arises due to the damage to the vestibular branch of the 8th cranial nerve (vestibulocochlear nerve). The auditory branch is affected less frequently. The disturbances start from noise in ears. At that moment, the drug use should be stopped.

Streptomycin is a nephrotoxic agent. Also, the drug inhibits neuromyscular transmission that can result in respiratory depression.

Streptomycin is contraindicated in renal failure, severe forms of cardiovascular failure, disorders of cerebrovascular circulation, myasthenia gravis, and diseases of vestibulocochlear nerve.

Vitamins of A, B group, and C are prescribed for prevention or reduction of streptomycin neurotoxicity. Also, streptomycin pantothenate or streptomycin ascorbate are used with the same purpose. Streptomycin is prescribed only for inpatients.

Kanamycin is another representative of aminoglycosides. The drug has broad antibacterial spectrum of action. Kanamycin is used in tuberculosis treatment in the case when other antituberculous drugs are ineffective.

Other Antibiotics

Cycloserine is an antibiotic with broad antibacterial spectrum, including Gram-positive and Gram-negative bacteria. The most valuable property of cycloserine is its activity against mycobacteria. The drug is active against both extracellular and intracellular mycobacteria. Cycloserine is used to treat tuberculosis as a reserve agent when other antituberculosis drugs become ineffective. Cycloserine is the drug with high neurotoxicity. Side effects of the drug are headache, dizziness, insomnia, irritability, memory loss, paresthesia, peripheral neuritis, anxiety, psychasthenic state

(a condition characterized by rapid mood changes, suicidality, depression, etc.), epileptiform seizures, loss of consciousness, etc.

Florimycin (viomycin) is a polypeptide antibiotic. The drug affects protein synthesis that results in bacteriostatic effect. The drug is characterized by low absorbability in the gastrointestinal tract, therefore it is administered intramuscularly. Florimycin easily penetrates through the tissue barriers. Viomycin is used to treat different forms of tuberculosis when other drugs are ineffective. The side effects of florimycin are the damage to VIII (vestibulocochlear) cranial nerve, disturbances of renal function, allergic reactions, and electrolyte disturbances.

Synthetic Drugs

Ethambutol is a synthetic agent with high antituberculosis activity. The drug affects only mycobacteria and is active in cases of bacterial resistance to isoniazid, streptomycin, and other drugs. Mechanism of action is based on ethambutol ability to inhibit the synthesis of RNA and proteins and the ability to interact with divalent metal ions. Also, ethambutol affects the ribosome structure. Ethambutol is bacteriostatic antitubercular agent. The drug is taken orally once a day after a meal. Ethambutol is easily absorbed from the gastrointestinal tract and excreted unchanged through the kidneys. Insignificant amount of the drug is excreted unchanged in feces.

Ethambutol is used in combination with other antituberculosis agents in treatment of different forms of tuberculosis. Side effects of ethambutol are dispepsia, dizziness, depression, allergic reactions, and visual field loss. Drug intake during 2–6 months may be accompanied by disturbances of color vision (especially perception of red and green colors). The vision is restored after drug removal.

Pyrazinamide is a derivative of pyrazincarbonic acid. The value of the drug is its ability to affect mycobacteria with resistance to other antituberculosis drugs. Antituberculosis activity of pyrazinamide is lower than the activity of isoniazid, rifampicin and aminoglycosides. Mechanism of pyrazinamide action is not

completely known. It is apparent that the drug inhibits mycobacteria development on the stage of intracellular division.

Pyrazinamide is easily absorbed in the gastrointestinal tract, penetrates into tuberculous foci and exhibits high activity in the acidic environment of caseous masses. Pyrazinamide is excreted through the kidneys. The drug is taken orally 3–4 times a day after a meal. Bacterial resistance to pyrazinamide develops readily. The drug is used to treat tuberculosis in combination with other antituberculosis drugs. Side effects are dispepsia, disturbances of liver functions, allergic reactions, artralgia, gout exacerbation, and photosensitization. Cyanocobalamin, methionine, and glucose are used to diminish pyrazinamide toxicity.

Ethionamide and *prothionamide* are isonicotinic acid derivatives. The mechanism of action of these drugs is the same as that with isoniazid. Their properties are close to the properties of isoniazid, but antituberculosis activity is low. Ethionamide and prothionamide are bacteriostatic agents, they are active against both extracellular and intracellular mycobacteria. Both drugs stimulate phagocytosis in the inflammatory foci. The value of these drugs is their ability to affect mycobacteria which are isoniazid-resistant. The drugs are taken orally or administered rectally 3–4 times a day, but in case of poor tolerance – 2 times a day. It is necessary to notice that patients tolerate prothionamide better. The side effects of ethionamide and prothionamide are nausea, vomiting, diarrhea, liver function disturbances, allergic reactions, insomnia, and orthostatic hypotension. For prevention or reduction of these side effects, pyridoxine and nicotinamide are used. Ethionamide and prothionamide are contraindicated in pregnancy.

Drugs with Moderate Antituberculosis Activity:

Para-Aminosalycilic Acid Derivatives

Sodium para-aminosalicylate (PAS) and *calcium para-petrolyl-aminosalicylate (Bepascum)* exhibit bacteriostatic effect against mycobacteria. The molecular structure of these drugs is similar to the structure of para-aminobenzoic acid (PABA).

Therefore, para-aminosalycilic acid derivatives are competitive antagonists of PABA. It is known that PABA is used by *Mycobacteria* for protein synthesis. Inhibition of protein synthesis by PAS and Bepascum slows down the growth and division of bacteria.

PAS is taken orally after meal (with milk or alkaline mineral water). The drug is easily absorbed from the gastrointestinal tract. After absorption, the drug quickly penetrates into tissues of the internal organs. About 90 % of the taken dose is excreted through the kidneys, 10 % – with bile in an inactive form. The main route of PAS inactivation is acetylation. Sometimes PAS is administered intravenously drop-by-drop.

Bepascum is a drug with prolonged action which releases para-aminosalycilic acid. The drug is taken orally.

Both drugs can cause such side effects as dispepsia (nausea, vomiting, diarrhea, and abdominal pain), allergic reactions (skin rash), hepatotoxicity, crystalluria, agranulocytosis, increased growth of the thyroid gland, and hypothyroidism.

Thiosemicarbazone Derivatives

Thiacetazone is a synthetic agent which is active against *M. tuberculosis* and *M. leprae*. The drug exerts bacteriostatic activity. Thiacetazone is taken orally after a meal. The clinical use of thiacetazone is restricted by its high toxicity. The drug is used only in combination with other antituberculosis agents in the treatment for extrapulmonary tuberculosis: tuberculosis of mucous and serous membranes, lymphadenitis, specific fistulas, etc.

Side effects of thiacetazone are headache, nausea, dermatitis, blood dyscrasias (anemia, thrombocytopenia, leukopenia, and agranulocytosis), and disturbances of liver and renal functions.

Table 19 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Isoniazidum	Orally 0.3 g 2–3 times daily; intramuscularly 0.3–0.9 g or intravenously drop-by-drop 0.01 g/kg (as 0.2 % solution) daily	Tablets 0.1 or 0.3 g; ampoules 5 ml of 10 % solution
Rifampicinum	Orally 0.45 g daily; intravenously drop-by-drop 0.45 g daily	Capsules 0.15 g; ampoules 0.15 g of powder for injections
Natrii para-aminosalicylas	Orally 3–4 g 3–4 times daily (1–2 teaspoons of granules); intravenously drop-by-drop 7.5–15 g daily (as 3 % solution)	Tablets 0.5 g; granules 100 g; vials 250 or 500 ml of 3 % solution
Ethambutolum	Orally 0.025 g/kg daily	Tablets 0.1 or 0.4 g
Streptomycini sulfas	Intramuscularly 0.5 g 2 times daily	Vials 0.5 g of powder for injections
Pirazinamidum	Orally 0.015–0.025 g/kg once a day or 0.05–0.07 g/kg 2–3 times per week	Tablets 0.5 or 0.75 g

Step 1. Tasks for Self-Control
Antisyphilitic Drugs. Antituberculosis Drugs

1. A 35-year-old man received antitubercular drug has acute pain onset of right big toe, swelling, and low-grade fever. Gouty arthritis was diagnosed and high serum uric acid level was found. Which of the following antituberculosis drugs are known for causing high uric acid levels?

A. Pyrazinamide.
B. Aminosalycylic acid.
C. Rifampicin.
D. Thioacetazone.
E. Cycloserine.

2. A patient has appealed to the doctor with complaints of red colour of urine and tears. It is known, that he is treated for pulmonary tuberculosis. What drug can cause this adverse effect?

A. Doxycycline.

B. Rifampicin.

C. Metronidazole.

D. Streptomycin sulfate.

E. Isoniazid.

3. The first-line drug for treatment of tuberculosis is prescribed to 38-year-old patient. It is known that drug causes several adverse effects, which are connected with oppressing of pyridoxalphosphate formation. Call this drug.

A. Isoniazid.

B. Rifampicin.

C. Doxycycline.

D. Metronidazole.

E. Chingaminum.

4. Neuritis of optic nerve occurred in the patient in result of treating with certain antituberculosis drug. Identify this drug.

A. Streptomycin.

B. Ethambutol.

C. Kanamycin.

D. Isoniazid.

E. Rifampicin.

5. It is known, that patient A. with pulmonary tuberculosis has hereditary insufficiency of N-acetyltransferase. Indicate the antituberculosis agent which can promote the development of marked toxic effects in this patient.

A. Sodium salt of PAS.

B. Streptomycin.

C. Ethambutol.

D. Isoniazid.

E. Rifampicin.

6. In clinical practice tuberculosis is treated with izoniazid – that is an antivitamin able to penetrate into the tuberculosis bacillus.

Tuberculostatic effect is induced by the interference with replication processes and oxidation-reduction reactions due to the buildup of pseudo-coenzyme:

A. NAD.
B. TDP.
C. FMN.
D. CoQ.
E. FAD.

7. A patient suffering from syphilis has been treated with bismuth preparations. As a result of it some grey spots turned up on the mucous membrane of the oral cavity; nephropathy symptoms were also present. What drug should be used for treatment of bismuth intoxication?

A. Methylene blue.
B. Naloxone.
C. Bemegride.
D. Unithiol.
E. Nalorphine.

ANTILEPROSY DRUGS

Leprosy is an infectious disease caused by *Mycobacterium leprae* (Hansen's bacillus). Drugs for leprosy treatment (antileprosy drugs) are classified into the following groups.

1. Derivatives of aromatic sulfones: DDS – *diaminodiphenyl sulfone (dapsone, avlosulfon), solusulfonum (sulphedrone, cimedone), dimociphone, diuciphone.*
2. Antibiotics:
   – rifamycins*: rifampicin*;
   – macrolides: *clarithromycin*;
   – tetracyclines: *minocycline.*
3. Fluoroquinolones: *ofloxacin (Tarivid).*
4. Synthetic antituberculosis drugs: *ethionamide, prothionamide, thioacetazone.*
5. Phenazine derivatives: *clofazimine (lamprene).*

Diaphenylsulfone (dapsone) is one of the main drugs for leprosy treatment. Dapsone is a competitive antagonist of para-aminobenzoic acid and due to this fact it influences the synthesis of folic acid by *Mycobacterium leprae*. Also, the drug activates lysosomes of macrophages. The drug is taken 0.05–0.1 g once a day six days a week. The drug is rapidly and almost completely absorbed from the gastrointestinal tract. The half-live for dapsone in the body is 24 hours. Side effects of dapsone are weakness, headache, dyspepsia, toxic hepatitis, precordialgia, hemolysis, and agranulocytosis. The toxicity of the drug is limited due to reduction of the dose and intake of B group vitamins and iron-preparations.

Diuciphone is a diphenyl sulfone derivative containing two residues of methyluracil. The drug has antileprosy and immunomodulating effects.

As a rule, antibiotics, ofloxacin, and synthetic antituberculosis agents in combination with sulfones are used to treat leprosy. The rapid effect is typical for rifampicin. Rifampicin is taken every day or twice a week (in combination with other antileprosy agents). Being located in the skin, *Mycobacterium leprae* lose their viability in 5 days. Synthetic antituberculosis drugs are less effective in leprosy treatment, but more toxic.

Clofazimine is a lipid-soluble phenazine derivative. The drug accumulates in the skin, gastrointestinal tract, and in the cells of monocyte macrophage sprout. Side effects are ichthyosis, skin dyschromia (red-brown skin), diarrhea, intestinal colic, etc. Clofazimine is contraindicated in pregnancy.

The chemotherapy of leprosy is a long-term cure. *Mycobacterium leprae* resistance and disease relaspse are common problems. A relapse in leprosy occurs due to persistent *Mycobacterium leprae* in bone marrow, nervous and muscular tissues. The combined antileprosy chemotherapy by means of 2–3 drugs with different chemical structure is used to prevent leprosy prolapse and antileprosy drug resistance. The most common drug combination includes diphenyl sulfone, rifampicin, and clofazimine. Besides, the use of immunomodulators and vitamins in treatment of leprosy is advisable.

ANTIVIRAL DRUGS

Antiviral drugs are agents of different chemical structure which interfere with viral penetration into the cells, synthesis of viral nucleic acids and proteins, and viral replication.

The following mechanisms of action are typical for different antiviral drugs:

1) inhibition of viral absorption and penetration into the host cell: *γ-globulin, enfuvirtide*;

2) impairment of the efficient release of the viral genome: *amantadine (midantanum), rimantadine*;

3) violation of viral protein synthesis: *guanidine, saquinavir*;

4) violation of nucleic acid synthesis: *zidovudine, acyclovir, vidarabine, idoxuridine*;

5) violation of the virion assembly: *metisazon*.

Nowadays, about 30 antiviral drugs are used in medicine. Except interferons, all of them are synthetic agents.

There are the following groups of antiviral drugs:

– drugs for influenza treatment;

– drugs active against cytomegalovirus and herpes simplex virus;

– drugs active against human immunodeficiency virus (HIV);

– drugs active against retrovirus and picornavirus;

– drugs affecting variola virus;

– drugs active against Hepatitis B and Hepatitis C viruses.

Drugs for Influenza Treatment

This group is reffered by the following drugs.

1. Drugs which block viral M_2 proton channel: *rimantadine, amantadine,* and *adapromine.*

2. Drugs which inhibit viral enzyme neuraminidase: *zanamivir, oseltamivir.*

3. Drugs which inhibit viral RNA-polymerase: *ribavirin.*

4. Other drugs: *arbidol, oxoline.*

The Matrix-2 (M_2) protein is a specific protein of influenza virus. This protein is located in viral membrane and functions as an ionic channel. Drugs blocking this protein affect the disassembling of the virus and prevent the release of the viral genome in the host cells. Due to this, viral replication is abolished.

Amantadine (midantanum) is used to prevent influenza type A. However, the drug has low efficiancy to use it with that end in view. The drug is taken in dose 100 mg twice a day (every 12 hours). Amantadine is readily absorbed in the gastrointestinal tract and excreted from the body with urine.

Adapromine and *rimantadine* are more effective agents. Rimantadine is active against influenza type A virus (especially type A_2). Adapromine is active against influenza A and B type viruses. Also, rimantadine affects the tick-borne encephalitis virus. For prevention of influenza, rimantadine is taken orally in dose 0.05 g, adapromine – in dose 0.1 g once a day during 10–20 days. Timely drug intake reduces the frequency of the disease incidence by 50 % and more. In case of taking influenza, it is mild. It is necessary to notice that intake of the drugs in 2–3 days after the disease onset has low efficiency. The drug intake in 5 days after the start of the disease is completly ineffective. For prevention of tick-borne encephalitis, rimantadine is taken twice a day in dose 0.1 g during 3–5 days. Preventive drug intake starts immediately after a tick bite. Rimantadine is readily absorbed in the gastrointestinal tract, metabolized in the liver, and excreted through the kidneys. As a rule, the drug is well tolerated by patients. Side effects include dyspepsia, headache, insomnia, dizziness, and irritability. Rimantadine has teratogenic and embryotoxic effects. Adapromine is a less toxic agent. Both drugs are contraindicated in acute hepatic and renal diseases and during pregnancy.

Influenza viruses quickly develop resistance to the drugs of this group.

Neuraminidase is a glycoprotein which is located on the surface of the influenza viruse types A and B. The enzyme promotes penetration of the virus into the target cells in the respiratory tract.

The drugs, blocking neuraminidase, violate the virus propagation and affect the viral replication. *Zanamivir* and *oseltamivir* are drugs with such mechanism of action.

Zanamivir is used for intranasal application or for inhalations. About 15 % of administered dose of zanamivir penetrates into the systemic blood circulation. The drug is excreted through the kidneys.

Oseltamivir (Tamiflu) is taken orally. The drug is active against influenza viruses types A and B, including virus AH4N2. Oseltamivir is readily absorbed in the gastrointestinal tract. The drug undergoes fast hydrolysis in the intestine, liver, and blood. Bioavailability of its active metabolites is about 80 %. The main route of excretion is the kidneys. The half-life period is 6–10 hours. Side effects of oseltamivir are nausea, vomiting, and nephrotoxicity.

Ribavirin is a derivative of guanosine. The drug is phosphorylated in the body into ribavirin monophosphate and ribavirin triphosphate. Ribavirin monophosphate inhibits the synthesis of guanine nucleotides. Ribavirin triphosphate inhibits viral RNA-polymerase and affects the formation of iRNA. Ribavirin is active against influenza viruses A and B. Also, the drug is used in treatment of severe infections caused by respiratory syncytial virus and hemorrhagic fever with renal syndrome. Side effects of ribavirin are skin rash and conjunctivitis. Ribavirin has mutagenic, teratogenic, and cancerogenic properties.

Arbidol is used to prevent and treat influenza type A and B, acute respiratory viral infections, and herpes recurrent infection. Arbidol exhibits interferonogenic activity, stimulates cellular and humoral immunity. The drug is taken orally and tolerated by patients well.

Oxoline is used to prevent influenza and to treat viral rhinitis, adenoviral keratoconjunctivitis, herpetic keratitis, and some viral skin diseases (shingles, etc.). Oxolinic ointment is used to lubricate nasal mucosa, to apply over the lower eyelid, or on the skin.

Antiherpethetic Drugs and Drugs for Cytomegalovirus Infection Treatment

The following drugs are used to treat herpes.

1. Drugs for resorbtive action: *acyclovir, valacyclovir, famcyclovir, vidarabine*.

2. Drugs for topical use: *trifluridine, idoxuridine, megosin, gossypol*.

Acyclovir (Zovirax) is a drug of high activity. It is a synthetic purine nucleoside analogue. In a human body, acyclovir is phosphorylated with active metabolite formation. Phosphorylated acyclovir inhibits DNA-polymerase. It results in violation of nucleic acid synthesis and inhibition of viral replication. It should be noticed that viral DNA-polymerase is 100 times more sensitive to acyclovir action than human DNA-polymerase. The oral bioavailability of acyclovir is about 20 %. Acyclovir has satisfactory permeability through the blood-brain barrier. The therapeutic indications for acyclovir are herpes simplex, herpetic lesions of eyes and genitalia, and cytomegalovirus infection. The drug is taken orally, administered intravenously, or applied topically (5 % skin cream, or 3 % ophthalmic ointment which are used 5 times a day). In case of significant skin damage, acyclovir is taken orally 5 times a day in dose 0.2–0.4 g. Intravenous acyclovir is used to treat herpetic infections in patients with immunodeficiency or to treat severe herpetic lesions of genitalia. Side effects develop seldom. During acyclovir therapy the following side effects are observed: nausea, vomiting, diarrhea, headache, and allergic reactions. Intravenous acyclovir administration can cause the reversible neurological complications (hallucination, excitement, and confusion), renal dysfunction, phlebitis, and skin rash. External acyclovir application can cause dry and peeling skin.

Valacyclovir is a new agent for treatment of herpetic infection. Oral bioavailability of valacyclovir is about 54 %. It is necessary to notice that valacyclovir has no antiviral activity. Valacyclovir is converted to acyclovir in the intestine and liver.

Famcyclovir and *ganciclovir* are similar to acyclovir.

Vidarabine is phosphorylated by kinases into the active metabolite. Phosphorylated metabolite inhibits viral DNA-polymerase and suppresses the virus replication. Vidarabine is used to treat herpetic encephalitis. The drug decreases the mortality from this disease by 30–70 %. Sometimes, vidarabine is used to treat shingles and herpetic keratoconjunctivitis. Also, vidarabine is used to treat patients suffering from allergic reactions to idoxuridine. Side effects of vidarabine are dyspepsia, tremor, psychosis, allergic reactions, blood clots on the injection site.

Idoxuridine and *trifluridine* are antiherpetic drugs which are used topically. Therapeutic indications for their use are herpetic keratitis and keratoconjunctivitis. Side effects are irritation of mucous membranes and eyelid oedema.

Ganciclovir, valganciclovir, foscarnet, and *Vitravene (fomivirsen)* are drugs for treatment of cytomegalovirus infection.

Mechanism of action of ganciclovir is similar to acyclovir. The drug is used to treat cytomegalovirus retinitis, colitis, esophagitis, pneumonia, etc. Ganciclovir is administered intravenously or used topically in conjunctival cavity. The side effects of ganciclovir are headache, psychosis, convulsions, liver damage, granulocytopenia, thrombocytopenia, and skin rash. Ganciclovir is a drug with teratogenic activity.

Valganciclovir is metabolized to gancyclovir in the intestine and liver. The bioavailability of valganciclovir is about 60 % (in 10–12 times higher than ganciclovir).

Foscarnet is a drug with the same mechanism of action. The drug is used to treat cytomegalovirus retinitis in patients with AIDS. Also, foscarnet may be used as an alternative to acyclovir to treat herpes simplex and shingles. Foscarnet is administered intravenously or applied topically in ointment. The toxicity of foscarnet is higher than gancyclovir toxicity. But foscarnet inhibits the leukopoiesis to a lesser degree than gancyclovir. Side effects of foscarnet are fever, headache, convulsions, nephrotoxicity, cardiac arrhythmias, encephalopathy, disturbances of mineral and electrolyte balance, etc.

Vitravene is used to treat cytomegalovirus rhinitis and retinitis.

Drugs Active Against Human Immunodeficiency Virus (Antiretroviral Drugs)

The following drugs are used to treat HIV-infection:

1. Reverse transcriptase inhibitors.

1.1. Nucleosides: *zidovudine, didanosine, stavudine,* and *zalcitabine.*

1.2. Non-nucleoside compounds: *nevirapine, delavirdine,* and *efavirenz.*

2. HIV protease inhibitors: *indinavir, ritonavir, saquinavir,* and *nelfinavir.*

The synthesis of viral DNA on the matrix (viral RNA) occurs after penetration of AIDS virus into lymphocytes. This synthesis is controlled by reverse transcriptase. After phosphorylation, zidovudine blocks reverse transcriptase and inhibits DNA synthesis. This results in inhibition of iRNA and viral protein synthesis. *Zidovudine* is effective mainly against virus carriers (before the appearance of AIDS symptoms). In sick patients, zidovudine slows down the disease progression, prolongs the duration of life, and reduces the frequency and severity of infectious complications. But recovery does not complete. Zidovudine is taken orally 0.1 g 5–6 times a day or 0.2 g 3 times a day. The drug is readily absorbed in the gastrointestinal tract. Zidovudine readily penetrates through the blood-brain barrier. About 75 % of administered dose is metabolized in the liver. The main route of zidovudine excretion is through the kidneys. The prolonged therapy with zidovudine (more than 6 months) results in development of antiviral drug resistance. Side effects of zidovudine are anemia, neutropenia, thrombocytopenia, pancytopenia, headache, diarrhea, fever, and renal dysfunction. After prolonged use of zidovudine, the following drugs may be prescribed to a patient: didanosine, zalcitabine, stavudine, lamivudine, or abacavir. These drugs have an identical mechanism of action with zidovudine. All drugs are taken orally and undergo hepatic metabolism with the subsequent renal excretion. Hematotoxicity (thrombocytopenia, leukopenia, and anemia), neurotoxicity (headache and insomnia), and renal, pancreatic and hepatic dysfunctions are typical side effects of these drugs.

The non-nucleoside agents for AIDS treatment are *nevirapine, delavirdine,* and *efavirenz*. These drugs also block reverse transcriptase, but bind to enzyme in another site than nucleosides. There is an evidence that these drugs also simultaneously inhibit DNA-polymerase. Non-nucleoside drugs are taken orally and used only in HIV-1 infection.

HIV protease inhibitors (*indinavir, ritonavir, saquinavir, nelfinavir*) block enzymes regulating formation of structural proteins and enzymes which are necessary for virus replication. The deficit of these proteins results in formation of virus immature precursors and slows down the development of infection. Saquinavir is the most commonly used HIV protease inhibitor. The drug is effective against both HIV-1 and HIV-2 infections. Saquinavir is taken orally. The bioavailability of the drug is very low (about 4 %), but blood concentration of the drug is enough to inhibit retroviral replication. The side effects of saquinavir are dyspepsia, disturbances of lipid and carbohydrate metabolism, anemia, and dysuria. The prolonged drug intake causes the development of antiviral drug resistance.

Co-formulated drug use is the most effective in HIV therapy: zidovudine + zalcitabine + saquinavir, zidovudine + saquinavir, etc.

Drugs Active Against Variola Virus

Metisazon is used to prevent smallpox and to decrease the risk of vaccine complication. Metisazon may act by inhibiting viral structural protein synthesis or blocking late stages of virus assembly. The drug is taken orally. Side effects include dyspeptic disorders and dizziness.

Broad Spectrum Antiviral Drugs (Including Hepatitis B and C Viruses)

Interferons are recovered from the cultures of human leukocytes (*α-interferon*), fibroblasts (*β-interferon*), or lymphocytes (*γ-interferon*). Recombinant interferons are derived by means of implantation of correspondent human genes to *Escherichia coli.*

Interferons are species-specific low molecular weight glycoproteins. Interferons are not themselves antiviral active.

Interferon interacts with a specific receptor located on the cellular surface that results in activation of protein kinase and formation of low-molecular inhibitor of protein synthesis. This inhibitor acts due to stimulation of enzymes which destroy RNA of viruses and host cells.

Besides antiviral and antibacterial effects, interferons also activate the immunity (phagocytic activity of macrophages and toxicity of killers increase), exhibit antitumor and radioprotective activity, and influence functions of different systems of the body, including CNS.

There is the following classification of interferon preparations:

– α-2A-interferons: *Reaferon, Roferon-A, Laferon*;
– α-2B-inteferons: *Intron-A, Viferon*;
– α-2C-interferons: *Berofor, Wellferon*;
– β-interferons: *Betaseron (Betaferon), Feron*;
– γ-interferons: *Gammaferon, Imunoferon.*

Alfa-interferons (α-2A, α-2B) are used mainly as antiviral drugs. These drugs are effective in treatment of herpetic keratitis, herpetic lessions of the skin and sex organs, acute respiratory viral infection, shingles, viral hepatitis B and C, and AIDS.

Laferon and *Reaferon* are used topically as nasal or eye drops (to prevent a disease – 2–3 drops in nose or in conjunctival cavity 1–2 times a day; to treat the disease – 4–6 times a day). The drugs are also used topically to treat shingles.

There are high-purified interferons (1 mg – 5 000 000 IU) for oral intake or for parenteral administration (intravenously, intramuscularly, intraosseously, endolymphatically, and endolumbarly). Interferons are quickly inactivated, therefore they are administered 4–6 times a day. High-purified interferons are used in treatment for systemic viral infections or malignant neoplasms. Recombinant interferons (*Reaferon*, *Roferon*, *Intron-A*, *Viferon*, and *Wellferon*) are administered 2–3 times a day. Moreover, the drugs may be administered rectally. Side effects are possible in case of parenteral interferon administration and include fever, headache, muscular pain, reduction of blood pressure, cardiac arrhythmias, paresis and paralisis, blood dyscrasias, and dyspepsia.

A disadvantage of interferon therapy is the development of drug resistance after 1–2 injections. The combined use of several inductors of interferons is recommended to prevent it.

Interferon inductors are drugs which stimulate the formation of interferons. There are natural (bacteria, viruses, rickettsia, fungi, etc.) and synthetic (vitamins, synthetic polynucleotides, polyanions, and some low-molecular-wheight and high-molecular-wheigh compounds). The representatives of synthetic low-molecular-wheight interferon inductors are *Amixin (tilorone)*, *mefenamic acid*, *megosin*, etc. The representative of high-molecular-wheight interferon inductors is *poludanum*. Poludanum is used in eye drops for treatment of viral lesions of mucous membranes of the eyes. Also, poludanum is administered subcutaneously once a week in treatment for chronic hepatitis C. Mefenamic acid is used to treat influenza. Megosin is applied topically to treat viral skin diseases. Tilorone is used to treat influenza, acute respiratory viral diseases, hepatitis B and C, herpes, cytomegalovirus infections, neurotropic viral infections, tuberculosis, and chlamydiosis. This drug is contraindicated to pregnant women.

Some drugs of other pharmacological groups also exhibit the property to induce interferon formation. They are *levamisole*, *isoprinosine, dipyridamole, theophylline, bendazol (dibazol), Trental (pentoxifylline),* etc.

Beta-interferon is used in treatment of multiple sclerosis. It is a disease caused by demyelination of nervous fibers in the central nervous system. Multiple sclerosis occurs to young people, progressively worses, and results in disability. Recently, *Betaseron* was established by means of gene engineering. The drug significantly reduces the frequency and severity of the exacerbations and slows down the disease progressing. Betaseron is administered subcutaneously once every 48 hours. Side effects of betaseron are pain and redness on the injection site, fever, weakness, muscle pain, anemia, thrombocytopenia, neutropenia, lymphopenia, and menstrual irregularities.

Table 20 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Oxolinum	Topically to apply to the nasal mucosa 2 times daily; 1–2 drops in each eye 5–6 times daily	Ointment 0.25 % or 0.5 % 10.0 or 15.0 g; eye drops: 0.1 % solution 10 ml
Remantadinum	Orally 0.1 g 1–3 times daily	Tablets 0.05 g
Azidothimidinum (Zidovudine)	Orally 0.1 g 5–6 times a day or 0.2 g 3 times a day	Capsules 0.1 or 0.25 g
Aciclovir	Orally 0.2–0.8 g 4–5 times a day; intravenously slowly 0.000 5–0.001 g/kg 3 times daily; topically to treat skin infections; for instillation into a lower conjunctival sac 5 times a day	Tablets 0.2; 0.4 or 0.8 g; vials 0.25 g of powder for injections; ointment 5 % 5 g; eye ointment 3 % 4.5 g or 5 g
Laferon	For instillation into the nose (3–6 drops) or eyes (1–2 drops) (before using, the powder of the ampoule is dissolved in 2 ml of sterile water) 3–6 times daily; intramuscularly, subcutaneously or intravenously 1 000 000–5 000 000 IU 1–2 times daily	Ampoules or vials with powder 1 000 000; 3 000 000 or 5 000 000 IU (dissolved before administration)

ANTIPROTOZOAL DRUGS

It is known that more than 1 000 species of protozoa are pathogenic for humans. Antiprotozoal drugs are selectively active against protozoa – causative agents of malaria, amoebiasis, giardiasis, toxoplasmosis, leishmaniasis, trichomoniasis, and balantidiasis. Antiprotozoal drugs include synthetic agents and some antibiotics, and they are classified into the following groups.

1. Antimalarial drugs.
2. Drugs for giardiasis treatment.
3. Drugs for toxoplasmosis treatment.
4. Drugs for balantidiasis treatment.
5. Drugs for trichomoniasis treatment.
6. Drugs for leishmaniasis treatment.

Antimalarial Drugs

In the past, malaria was one of the most common diseases in the world. About one million peple were dying every year. In 50–60s of the 20th century, malaria morbidity was significantly reduced due to the broadest antimalarial actions under UN auspices. Unfortunatelly, last years the formation of drug resistant strains of Plasmodium results in the increase of malaria morbidity.

A source of malaria infection is the sick person or a gamete carrier. A person can get infection through the bite of infected mosquitoes (seldom – due to blood transfusion from the sick person). Thus malaria parasites enter the blood.

There are 4 species of malaria parasites:

– *Plasmodium vivax*, and *Plasmodium ovale* – the causative agents of vivax (three-day malaria);

– *Plasmodium malaria* – the causative agent of quartan (four-day malaria);

– *Plasmodium falciparum* – the causative agent of tropical malaria.

Plasmodium ovale is found only in the tropics.

The Plasmodium parasite undergoes two cycles of replication: asexual cycle (schizogony) takes place in the human body, and sexual cycle (sporogony) occurs in the mosquito. Due to infected mosquito bite, the sporozoites enter the blood of the person, then quickly enter hepatocytes. Inside hepatocites, multiplication occurs: pre-erythrocytic or exo-erythrocytic schizogony stage. Tens of thousands of merozoites are formed due to multiple division of one sporozoit. Pre-erythrocytic schizogony is asymptomatic. After completion of pre-erythrocytic schizogony, merozoites penetrate into erythrocytes and undergo the stage of erythrocytic schizogony. This stage is accompanied by erythrocyte rupture and fever attacks. Erythrocytic merozoites again penetrate into erythrocytes and repeat the erythrocytic cycle. In infection with *Pl. vivax* and *Pl. ovale*, these cyclical fevers occur every 48 hours, in infection with *Pl. malarie* – every 72 hours, and in infection with *Pl. falciparum* – every 6 hours. Along with asexual division, the sexual forms of Plasmodium are

formed in the human blood. These sexual forms are called gametocytes (gamonts). Their presence in the blood is not accompanied by the disease symptoms, but gamonts are dangerous in the context of epidemiology. Such patients are the source of mosquito infection.

In the tropical and four-day malaria, after the completion of pre-erythrocytic schizogony, merozoites enter the blood and their following development occurs only in the erythrocytes. In the three-day malaria, the infection by genetically heterogeneous set of parasites occurs. A part of them (tachysporozoites or primary forms) pass the stage of tissue schizogony after penetration into hepatocytes and are released from the liver after completion of this stage. Another part of sporozoites (bradysporozoites or secondary forms) are capable to be in liver in dormant form from 8–9 months up to 2 years. After completion of the latent period, these dormant sporozoites undergo exoerythrocytic schizogony which finishes when parasites enter the blood and develop primary malaria or its relapse.

The duration of sporogony, exo- and erythrocytic schizogony, the ability of drug-resistant Plasmodium to appear are different for different species of Plasmodium.

Presently, the following chemical groups of drugs are used to treat malaria.

1. Quinoline derivatives: *quinine, chloroquine (chingaminum), mefloquine, primaquine,* and *quinocide.*
2. Biguanides: *bigumal.*
3. Pyrimidine derivatives: *chloridinum (pyrimethamine).*
4. 9-aminoacridine derivatives: *quinacrine.*
5. Sulfonamides.
6. Sulfones.
7. Tetracyclines.

Pharmaceutical industry produces a lot of co-formulated drugs: *Metakelfin* (contains *pyrimethamine* and *sulfalen*), *Fansidar* (contains *pyrimethamine* and *sulfadoxine*), *Fansimef* (contains *mefloquine, sulfadoxine,* and *pyrimethamine*), etc.

According to antimalarial action, the drugs are divided into the following groups.

1. Blood schizonticides are the drugs active against erythrocytic forms of Plasmodium: *chingaminum (chloroquine), mefloquine, quinine.* Also, the following agents are used in co-formulated drugs: *hydroxychloroquine, chloridinum, bigumal, sulfadoxine,* and *doxycycline.*

These drugs eliminate schizonts from the peripheral blood after 3–5 days treatment. These drugs prevent and interrupt malaria attacks in the acute phase of the disease.

2. Tissue schizonticides are the drugs which affect tissue forms of Plasmodium. These drugs are divided into two groups:

– drugs active against tachysporozoites are tissue schizonticides which are active against pre-erythrocytic forms: *bigumal* and *chloridinum*; these drugs are used to prevent malaria;

– drugs active against bradysporozoites are tissue schizonticides which are active against para-erythrocytic forms of Plasmodium: *primaquine* and *quinocide*; these drugs are used to prevent malaria relapses.

3. Gametocides are the drugs which are active against sexual forms of Plasmodium. These drugs are divided into two groups:

– gametocides acting upon sexual forms of Plasmodium in human erythrocytes: *primaquine* and *quinocide*;

– drugs inhibiting the sporogony in the body of mosquito: *bigumal* and *chloridinum*.

These drugs are used for collective protection against malaria – prevention of disease transmission from the sick to healthy person through a mosquito bite. Due to the use of these agents, sporozoites are not formed in the mosquito body.

Blood Schizonticides

Quinine is an alkaloid found in the bark of the cinchona tree. Different species of cinchona tree are native to South America. In the 17th century, the bark of the cinchona tree was brought to Europe and since then it was used to treat malaria as well as fever.

In 1816 quinine was isolated from the bark by Jeff Giese. Other antimalarial drugs were synthezied later on.

Quinine affects erythrocytic schizonts of Plasmodium, gamonts, pre-erythrocytic forms of *P. falciparum*, and the causative agent of toxoplasmosis. The drug is readily absorbed from the gastrointestinal tract and quickly excreted from the body. Quinine inhibits the centre of thermoregulation and decreases the body temperature in fever. Also, quinine inhibits the excitability of myocardium, exhibits negative chronotropic effect, stimulates uterine contractions in pregnant women, and stimulates the spleen to contract. Mechanism of action of quinine is identical with chingaminum, primaquine, quinocide, and mefloquine. This mechanism is associated with violation of DNA synthesis both in Plasmodium cells and in host cells. Besides, quinine seals the lysosomal membranes, resulting in impaired assimilation of hemoglobin by Plasmodium.

Therapy with quinine is commonly accompanied by side effects: dizziness, vomiting, headache, collapse, tinnitus, etc. Presently, quinine is once again being used to treat tropical malaria, because Plasmodium infections became resistant to other drugs.

Chingaminum (chloroquine) hes been suggested for malaria treatment in 1943. The drug is one of the best blood schizonticides. Chloroquine interrupts the acute malarial fever within 24–48 hours. Plasmodium infections disappear from the peripheral blood in 2–3 weeks after the start of therapy with chingaminum. The drug is used to prevent and treat all types of malaria.

Along with antimalarial effect, chloroquine exerts anti-inflammatory activity and is widely used to treat polyarthritis, systemic lupus erythematosus, scleroderma, and other collagen-vascular diseases. Also, chingaminum is used to treat amebiasis.

Chingaminum is taken orally and administered intramuscularly or intravenously. The drug is readily absorbed from the gastrointestinal tract. About 50 % of the drug bind to plasma proteins. The elimination rate for the drug is low. Kidneys are the main route of chingaminum excretion. Chloroquine side effects are headache, nausea, dermatitis, and loss of appetite. Its overdose can

cause dystrophy of myocardium and liver, tinnitus, disturbances of accommodation, and leukopenia.

Mefloquine is an active antimalarial agent. In tropical malaria, the single use of the drug interrupts malarial fever and kills chloroquine-resistant strains of Plasmodium. Mefloquine is also effective in three-day malaria but does not prevent relapse. The toxicity of mefloquine is low. Sometimes, therapy with mefloquine can result in nausea, vomiting, abdominal pain, and drowsiness. Central nervous system disorders are seldom possible (depression, halucinations, convulsions, and disorientation).

Chloridinum (pyrimethamine) is a synthetic agent – derivative of pyrimidine. The drug violates the synthesis of dihydrofolic acid due to the inhibition of dihydrofolate reductase. Pyrimethamine is active against erythrocytic and pre-erythrocytic forms of Plasmodium, and also inhibits the sporogony in the body of mosquito. Pyrimethamine is taken orally and easily absorbed from the gastrointestinal tract. The drug is able to accumulate in tissues and, therefore, has the prolonged effect. The therapeutic indications for chloridinum are treatment of malaria, toxoplasmosis, and leishmaniasis. Also, the drug is used for personal protection against malaria. The side effects include headache, dizziness, discomfort in the heart area, hepatic disfunction, megaloblastic anemia, leukopenia, and teratogenic effect.

Sulfonamides and sulfones are also blood schizonticides. These drugs affect utilization of benzoic acid by Plasmodium. The activity of these agents are relatively low and their antimalarial effect develops slowly. Sulfonamides and sulfones in combination with other drugs are used to treat malaria.

Tissue Schizonticides

Chloridinum (pyrimethamine) and *bigumal* are active against pre-erythrocytic forms (tachysporozoites). Both drugs inhibit dihydrofolic acid reductase that results in violation of terahydrofolic acid and nucleic acid synthesis.

Bigumal is a biguanide derivative. The drug is active against pre-erythrocytic forms and gamonts of Plasmodium. The activity of bigumal is lower than the activity of chloridinum. Bigumal is taken orally, readily absorbed from the gastrointestinal tract, and is readily excreted from the body. The therapeutic effect of bigumal develops slowly. The side effects are leukocytosis and erythrocyturia. It is necessary to notice that Plasmodium quickly develops the tolerance to bigumal.

Primaquine and *quinocide* are tissue schizonticides which are active against para-erythrocytic forms of Plasmodium (bradysporozoites). Primaquine affects bradysporozoites of *Pl. vivax* and *Pl. ovale* which cause the relapse. Also, primaquine affects the sexual forms of *Pl. vivax*, *Pl. ovale,* and *Pl. falciparum* in human erythrocytes. Primaquine is taken orally and well absorbed from the gastrointestinal tract. Maximal concentration in the blood is observed in 2 hours after drug intake. The drug is metabolized in the body and excreted through the kidneys. Therapeutic indications for primaquine are prevention of relapses of three-day malaria and prevention of malaria spreading through the carrier. Primaquine is commonly combined with other antimalarial drugs. Side effects of primaquine are dyspepsia, methemoglobinemia, leukocytosis or leukopenia.

Quinocide is more toxic than primaquine. Other antimalarial agents increase its toxicity, therefore, combined use of quinocide with them is impossible. Quinocide is taken orally 1–2 times a day after a meal. Side effects of quinocide are nausea, cyanosis, fever, irritation of bladder, leukopenia or leukocytosis. These complications disappear after giving up the drug.

Gametocides

Gametocides are drugs which are active against sexual forms of Plasmodium. Gametocides which inhibit the sexual forms of Plasmodium in human erythrocytes are *primaquine* and *quinocide*. Gametocides inhibiting the sporogony in the body of mosquito are bigumal and chloridinum. Pharmacology of these drugs is described above.

Selection Criteria for Antimalarial Drugs

Antimalarial drugs are used to treat and prevent malaria. In acute period (malarial fever, malarial coma), blood schizonticides are used (chingaminum (chloroquine), mefloquine, quinine, etc.). These drugs readily penetrate human erythrocytes and facilitate the fast improvement in clinical findings. The resistance of Plasmodium to these drugs develops relatively slow. In malarial coma, chloroquine and quinine are administered parenterally.

The reserve group (used in case of Plasmodium resistance to the main drugs) includes such drugs as pyrimethamine, bigumal, primaquine, quinocide, sulfonamides, sulfones, and tetracyclines. These drugs are less effective in comparison with main drugs. Their effect develops slowly, while resistance of Plasmodium develops quickly. Therefore, drug combinations with different mechanism of action are commonly used.

Primaquine is used to prevent relapse of three-day and four-day malaria.

The drugs influencing upon pre-erythrocytic forms of Plasmodium (for instance, pyrimethamine) are used for individual preventive chemotherapy in people who live in or travel to malaria risk areas. Blood schizonticides (chloroquine, mefloquine, etc.) are also sometimes used with this end in view.

The total preventive chemotherapy of malaria suggests the prevention of malaria transmission from the sick person to healthy people through mosquito bite. Gametocides (primaquine, pyrimethamine, and quinocide) are used for this purpose – to prevent formation of sporozoites in mosquito.

Drugs for Amebiasis Treatment

The causative agent of amebiasis is *Entamoeba histolytica*, which exists in two forms: vegetative and cystic. The transformation of vegetative form into cystic occurs in the presence of anaerobic bacterial flora (clostridium). Cystic forms, in turn, transform into vegetative amoeba, living in the intestinal lumen (without symptoms)

and feeding on the organic wastes of bacterial origin. Under the influence of aerobic bacteria (E. coli), amoeba takes on pathogenic properties. Vegetative forms of amoeba secrete proteolytic enzyme which dissolves tissues. It provides the formation of invasive forms of amoeba – hematophagous amoebas. A significant amount of erythrocytes is observed in the endoplasma of invasive forms of amoeba. At this stage, the invasive amoebiasis develops when amoeba is present both in the intestinal lumen and in the intestinal wall. By hematogenic way, amoeba can penetrate into the liver, lungs, and other organs.

Treatment of amebiasis differs depending on amoeba localization.

The drugs which are used to treat amoebiasis are classified as follows.

1. Drugs which are effective in any localization of amoeba: *metronidazole*.
2. Drugs of dirrect action which are effective against amoeba localized in the intestinal lumen: *chiniofonum* and *intetrix*.
3. Drugs of indirect action which are effective against amoeba localized in the both intestinal lumen and intestinal wall: *tetracyclines*.
4. Drugs acting upon amoeba which is mainly located in the intestinal wall and liver: *emetine hydrochloride*.
5. Drugs which are mainly effective against amoeba localized in the liver: *chloroquine*.

Metronidazole is a drug which is effective in any localization of amoeba. The drug was introduced in the medical practice in 1951 as an agent for the treatment of trichomoniasis. Metronidazole is also active against amoeba, giardia, balantidium, and *Helicobacter pylori*. Metronidazole is not active against cystic forms of amoeba. The drug is taken orally 0.25–0.5 g three times a day after a meal. Metronidazole is readily absorbed from the gastrointestinal tract and is well metabolized. The main route for drug excretion is via kidneys. Insignificant amount of metronidazole is excreted by salivary glands, intestine, and mammary glands. Metronidazole is manufactured in

tablets, solution for intravenous administration, and vaginal suppositories. Side effects of metronidazole are nausea, diarrhea, metallic taste in mouth, appetite loss, tremor, and disturbances of accommodation. Sometime, lesions of skin and mucous membranes are possible. Efficacy of metronidazole is low in localization of amoeba in the intestinal lumen. In this case, metronidazole is combined with chiniofonum. It is necessary to notice that metronidazole inhibits the activity of acetaldehyde dehydrogenase and causes accumulation of acetaldehyde that results in alcohol intolerance.

Chiniofonum (yatren) affects the vegetative and cystic forms of amoeba located in the intestinal lumen. The drug is taken orally. Gastrointestinal absorption of chiniofonum is low (about 10–15 %), therefore, high drug concentration is created in the intestinal lumen. Toxicity of yatren is low. Chiniofonum also exhibits significant antibacterial and antifungal activity. The drug is used to treat amebic dysentery, colitis, and uretritis. Ointments and solutions of chiniofonum are used externally in treatment for purulent wound, burns, ulcers, etc.

Intetrix is active against amoeba, *Candida*, Gram-positive and Gram-negative bacteria. The drug is used in treatment of intestinal amoebiasis and diarrhea. Toxicity of intetrix is low.

Tetracycline is an antibiotic which has indirect influence upon amoeba. Tetracycline affects the bacterial intestinal microflora which utilizes oxygen. Since species of amoeba are anaerobic, they can not live in the presense of oxigen. Therefore, tetracycline is an indirect amoebicide. Efficacy of tetracycline is lower than the efficacy of direct amoebicides. Aminoglycoside *monomicine* is also used to treat acute intestinal amoebiasis.

Emetine hydrochloride is an alkaloid of ipecacuanha. In therapeutic doses, emetine inhibits vegetative forms of amoeba but practically does not influence upon its cystic forms. The drug quickly eliminates the symptoms of amoebic dysentery, but does not prevent the relapses. Emetine is administered intramuscularly because oral intake of emetine significantly irritates the gastrointestinal mucosa.

Emetine is eliminated very slowly (more than a month), therefore, the drug is able to acummulate in the body. The main sites of emetine accumulation are the liver, lungs, and intestinal wall. Emetine does not penetrate the blood-brain barrier. Emetine is used in treatment for hepatic, pulmonary, and intestinal amoebiasis. The drug does not influence upon amoeba which is located in the intestinal lumen or in the brain. The side effects of emetine are nausea, vomiting, diarrhea, tachycardia, hypotension, precordialgia, polyneuritis, abnormal hepatic and renal functions, etc.

Chingaminum (chloroquine) is active against amoeba which is located in the liver, bacause the liver can accumulate a high concentration of the drug. The characteristics of chingaminum are given in subsection "Antimalarial drugs".

Drugs for Lambliasis Treatment

Lambliasis (giardiasis) is caused by *Lamblia intestinalis*. Parasites can damage the intestine with the following development of duodenitis and enteritis. Also, Lamblia can penetrate into the bile and pancreatic ducts. The following drugs are used to treat lambliasis: *metronidazole, albendazole (Vormil), furazolidone,* and *aminoquinol*.

Aminoquinol is a derivative of quinoline. The drug is used in treatment of lambliosis, toxoplasmosis, skin leishmaniasis, and systemic collagenosis. In lambliasis, aminoquinol is taken orally 20–30 minutes after a meal. After absorption, the drug is excreted with bile into the intestine. Simple drug intake results in excretion of the agent with bile during one month. The side effects of aminoquinol are dyspepsia, weakness, headache, tinnitus, insomnia, leukopenia, liver and kidney failure.

Pharmacology of albendazole is given in "Anthelmintic drugs".

Drugs for Trichomoniasis Treatment

A causative agent of trichomoniasis is *Trichomonas vaginalis*. The disease occurs in the form of colpitis or vulvovaginitis (in women), cystitis, stomatitis, colitis, and urethritis. The following drugs are used for trichomoniasis treatment:

– nitroimidazole derivatives: *metronidazole, tinidazole, ornidazole*;

– aminoquinoline derivatives: *trichomonacide*;

– imidazole derivatives: *econazole, nitazole, miconazole, clotrimazole*;

– nitrofuran derivatives: *furazolidone.*

Tinidazole (Fasigyn) exhibits high activity against *Trichomonas vaginalis*. Besides, the drug is active against obligate anaerobes. Tinidazole is readily absorbed from the gastrointestinal tract. The blood concentration of tinidazole is higher than the concentration of metronidazole. The duration of tinidazole action is much longer.

Trichomonacide has high activity against *Trichomonas vaginalis*. The drug is readily absorbed from the gastrointestinal tract. Trichomonacide is mainly used in treatment of urogenital trichomoniasis. The drug is taken orally or used topically in the form of suppositories or globules. Trichomonacide irritates the mucous membranes.

The pharmacological characteristics of imidazole derivatives (ornidazole, miconazole, econazole, clotrimazole) is given in "Antifungal drugs". Pharmacology of furazolidone is described in "Nitrofuranes".

Drugs for Toxoplasmosis Treatment

A causative agent of toxoplasmosis is *Toxoplasma gondii*. There are several forms of the disease which are accompanied by lessions of lymph nodes, intestine, lungs, eyes, central nervous system, and other organs. Toxoplasmosis can result in premature labor, abortion, congenital malformations, and stillbirth. To prevent congenital

toxoplasmosis, *chloridinum* and *aminoquinol* in combination with *sulfonamides* are prescribed to pregnant women. Preventive use of chloridinum and aminoquinol is contraindicated during the first 9 weeks of pregnancy due to their toxic influence upon the fetus. During this period, sulfonamides are used for prevention of fetal infection. *Chingaminum* and *pentamidine* are also used to treat toxoplasmosis.

Drugs for Balantidiasis Treatment

A causative agent of balantidiasis is infusorium *Balantidium coli* parasitizing the large intestine. *Tetracyclines* and *chiniofonum* are used to treat balantidiasis. Pharmacological characteristics of these agents are given in the corresponding sections.

Drugs for Leishmaniasis Treatment

Leishmaniasis is a protozoal disease which is caused by *Leishmania donovani* (the causative agent of visceral leishmaniasis – kala-azar) and *Leishmania tropica* (the causative agent of skin leishmaniasis). Visceral leishmaniasis is accompanied by high temperature, anemia, leukopenia, and splenomegaly. Initialy, leishmania parasites cause skin sores or ulcers at the site of the bite. If the disease progressies, it attacks the immune system.

Solusurminum is the most commonly used agent to treat visceral leishmaniasis. It is a preparation of pentavalent antimony. The drug is administered intravenously. Solusurminum blocks thiol groups of Leishmania enzymes that affects their growth and division. Side effects of solusurminum are nausea, headache, skin rash, and agranulocytosis. After an overdose of solusurminum, unithiol is administered as an antidote.

Sodium stibogluconate is also a preparation of pentavalent antimony. The drug is administered intramuscularly or intravenously. Its side effects are dyspepsia, vomiting, appetite loss, arterial hypotension, and chest pain.

Glukantim, pentakarinat (pentamidine), neostibazine, and *pentostim* are also preparations of pentavalent antimony for visceral leishmaniasis treatment.

Pentacarinat (pentamidine) is administered intramuscularly and in inhalations. Mechanism of drug action is associated with blocking thymidylate synthetase that inhibits of DNA synthesis. Pentakarinat is used to treat visceral and skin leishmaniasis, to prevent pneumonia in AIDS patients, and to treat trypanosomiasis, also known as African sleeping sickness. Side effects of pentakarinat are cough, dyspnea, bronchospasm, skin rash, metallic taste in the mouth, dizziness, arterial hypotension, acute pancreatitis, anemia, leukopenia, thrombocytopenia, increased blood urea nitrogen level and creatinine.

All above preparations of pentavalent antimony may be used to treat skin leishmaniasis. Also, the following agents are used to treat skin leishmaniasis: *quinacrine, monomycin, metronidazole, neomycin,* and *aminoquinol*.

Drugs for Trypanosomiasis Treatment

Causative agents of trypanosomosis are *Trypanosoma gambiense* and *Trypanosoma brucei rhodesiense* (sleeping sickness) and *Trypanosoma cruzi* (Chagas disease).

Melarsoprol is used as a primery agent for treatment of sleeping sickness. It is arsenicum derivative which easily penetrates through blood-brain barrier. Besides, *pentacarinat (pentamidine)* and *suramin* are used to treat African trypanosomosis. But these drugs do not penetrate into the central nervous system and, therefore, are effective only at early stages of the disease (when the brain is not affected by Trypanosoma). All these drugs are toxic and cause a large number of side effects.

To treat Chagas disease (spread in South America), *primaquine* and antibiotic *puromycin* are used.

Drugs for Chlamydiosis Treatment

Chlamydia are intracellular parasites of humans and animals. There are three species of Chlamydia which are causative agents for humans: *Chlamydia trachomatis, Chlamydia psittaci* and *Chlamydia pneumonia*. *Chlamydia trachomatis* is the most common sexually transmitted infection. *Chlamydia pneumonia* causes pneumonia. *Chlamydia psittici* mainly affects birds.

Chlamydia trachomatis can cause a recurrent ocular infection – trachoma. Other serological forms of *Chlamydia* cause lymphogranuloma venereum, conjunctivitis, child pneumonia, urethritis, endometritis, salpingitis, cervicitis, and epididymitis (inflammation of the epididymis). During pregnancy, *Chlamydia* can commonly cause premature labor and endometritis. Moreover, chlamydial infection may be associated with septic arthritis.

To treat chlamydiosis, *tetracycline* and *erythromycin* are aminly used. Penicillin is ineffective in that disease. Also, *rifampicin, chloramphenicol,* and *sulfonamides* are used. *Doxycycline* and *azithromycin* are drugs of choice for the treatment of urogenital chlamydiosis.

Table 21 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Chingaminum	Orally 0.25–0.5 g 1–2 times daily; intramuscularly or intravenously 0.5 g	Tablets 0.25 g; ampoules 5 ml of 5 % solution
Chloridinum	0.01 g 3 times daily 0.02 (for malaria treatment); 0.025 g 2–3 times daily (for toxoplasmosis treatment)	Tablets 0.01 or 0.025 g
Chinini hydrochloridum	Orally 0.5 g 2 times daily; subcutaneously 1.0 g 2 times daily; intravenously 1 ml in 20 ml of 40 % glucose solution	Tablets 0.25 or 0.5 g; ampoules 1 ml of 50 % solution

Continuation of the table 21

Drug name (Latin)	Single dose and route of administration	Drug product
Primachinum	Orally 0.009 g 3 times daily	Tablets 0.009 g
Metronidazolum	Orally 0.25–0.5 g 2–3 times daily; intravenously drop-by-drop 0.5 g 3 times daily	Tablets 0.25 g; bottles 100 ml of 0.5 % solution
Emethini hydrochloridum	Intramuscularly or subcutaneously 0.015 g twice a day	Ampoules 1 ml of 1 % solution
Furazolidonum	Orally 0.1 g 4 times daily	Tablets 0.05 g
Solusurminum	Intravenously slowly, intramuscularly or subcutaneously 0.1–0.12 g/kg once a day	Ampoules 10 ml of 20 % solution

ANTIFUNGAL DRUGS

Fungal infections (mycoses) are very common. Sick people, animals, and environment (plants, soil, etc.) can be the source of infection. Infection occurs through the injured skin, gastrointestinal tract, respiratory tract. Besides, potential pathogens, especially of the genus *Candida*, are located on the skin, in the upper respiratory system, on the mucous membranes of sex organs, and in the gastrointestinal tract. The cause of saprophytic flora transformation into pathogens is the reduction of the human body resistance due to immunodeficiency (at severe diseases, hormonal therapy, and the use of cytostatic drugs or some antibiotics).

Antifungal drugs are classified into the following groups.

1. Drugs for treatment of systemic or deep mycoses:
   – antibiotics: *amphotericin B, amphoglucaminum,* and *mycoheptin*;
   – azole derivatives: *miconazole, ketoconazole (nizoral), clotrimazole, itraconazole,* and *fluconazole.*
2. Drugs for treatment of dermatomycoses:

– antibiotics: *griseofulvin*;
– azole derivatives: *ketoconazole (nizoral), itraconazole, miconazole, fluconazole,* and *clotrimazole*;
– N-methylnaphthaline derivatives: *terbinafine (Lamisil)*;
– nitrophenol derivatives: *nitrofungin*;
– thiocarbamate derivatives: *chinofungin*;
– undecylenic acid derivatives: ointments *"Zincundanum"* and *"Undecinum"*;
– iodine preparations: *alcohol solution of iodine* and *potassium iodide*.

3. Drugs for treatment of mycoses caused by fungi Candida:
– antibiotics: *nystatin, levorin, amphotericin B,* and *natamycin (Pimafucin)*;
– azole derivatives: *itraconazole, clotrimazole, ketoconazole,* and *miconazole*;
– bis-quaternary ammonium salts: *decaminum*;
– halogens, non-organic acids, and alkalis.

Drugs for Systemic or Deep Mycosis Treatment

Systemic or deep mycoses affect the liver, bones and joints, gastrointestinal tract, brain and meninges, lymph nodes, etc. Sometimes, systemic mycoses develop in septic form. The deep mycoses are rare and difficult to treat. More than half of them are caused by saprophytic Candida activity. Less often, deep mycoses are caused by the causative agents of cryptococcosis, coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, blastomycosis, etc.

Amphotericin B is one of the main drugs for treatment of deep mycoses. It is a polyen antibiotic which is produced by *Streptomyces nodosum*. Amphotericin B does not affect bacteria, rickettsia, and viruses. Mechanism of action is associated with violation of transport function and permeability of fungi cell membrane. Selectivity of antifungal action occurs due to the fact that amphotericin B interacts with the main lipid of fungal cell wall – ergosterol. The main lipid of human and bacterial cells is cholesterol. Antifungal effect of

amphotericin B is characterized as fungistatic. This antibiotic is practically not absorbed in the gastrointestinal tract. Amphotericin B is administered intravenously and into body cavities, applied topically, and used in inhalations. The drug does not penetrate through the blood-brain barrier. About 95 % of the drug, circulating in the blood, bind to plasma proteins. The main organ of amphotericin B biotransformation is the liver. The drug elimination from the body is slow (about 20–40 % of administered dose during a week). The therapeutic indications for amphotericin B are hystomycosis, coccidioidomycosis, visceral candidomycosis, blastomycosis, and deep generalized trichophytosis.

Amphotericin B is a very toxic drug. Therefore, the drug is administered intravenously only in cases of life-threatening mycosis. Amphotericin B is dissolved by 5 % glucose solution and administered intravenously drop-by-drop during 3–6 hours. The drug is administered once in two days or twice a week. Side effects are headache, fever, dyspepsia, hypotension, nephrotoxicity, anemia, hypokalemia, disturbances of hepatic function, nephrotoxicity, thrombophlebitis, and allergic reactions. Amphotericin B is contraindicated in hepatic and renal diseases.

Despite identical mechanism of action, *amphoglucaminum* is a less toxic drug than amphotericin B. Amphoglucaminum is used to treat mycoses of the urinary, gastrointestinal, and respiratory tracts. The drug is administered during 10–14 days. To treat chronic (granulomatous) candidiasis and deep mycoses, amphoglucaminum is used during 3–4 weeks. Amphoglucaminum is taken orally. The drug is gradually absorbed from the gastrointestinal tract with maximum blood concentration in 2–3 days. Amphoglucaminum is excreted with urine during 10 days. Side effects are identical with amphotericin B but less expressed.

Mycoheptin has similar properties with amphotericin B. Mycoheptin is taken orally during 10–14 days or applied topically. The drug is partially absorbed in the gastrointestinal tract and excreted with urine. The therapeutic indications for mycoheptin are visceral mycoses, sepsis caused by Candida, aspergilosis, and

geotrichosis. Side effects are gastrointestinal distress, renal disfunction, and allergic reactions.

Miconazole is a derivative of imidazole. The drug is taken orally and administered intravenously or subarachnoidally to treat deep mycoses. Also, miconazole is applied topically to treat vaginal mucosa damage caused by Candida and for the treatment of dermatomycoses. The side effects of miconazole are thrombophlebitis, nausea, anemia, hyperlipidemia, hyponatremia, leukopenia, and allergic reactions.

Ketoconazole (Nizoral) is readily absorbed from the gastrointestinal tract. About 90 % of the absorbed drug bind to plasma proteins. The permeability of the drug through the blood-brain barrier is low. Ketoconazole is metabolized in the liver and excreted with urine and bile. The drug is used to treat deep mycoses and lesions of mucous membranes by Candida. Mechanism of action is associated with inhibition of ergosterol, triglyceride, and phospholipid biosynthesis that violates the structure of the fungal cell membrane. Side effects of ketoconazole are dyspepsia and hepatic dysfunction.

Itraconazole is a triazole derivative. The drug is taken orally. The drug absorption from the gastrointestinal tract is high, but permeability through the blood-brain barrier is low. Itraconazole is extensively metabolized by the liver. A large number of metabolites and unchanged itraconazole are excreted through the kidneys. Side effects are dyspepsia, headache, hepatic dysfunction, and allergic reactions.

Fluconazole is also a derivative of triazole. Fluconazole is one the most effective antifungal drugs. The drug is taken orally. Fluconazole easily penetrates through the blood-brain barrier. Unchanged fluconazole is excreted from the body through the kidneys. The therapeutic indications for fluconazole are fungal meningitis, coccidioidomycosis, candidomycosis, etc. Side effects of fluconazole are dyspepsia, hepatotoxicity, and skin allergy.

Drugs for Dermatomycosis Treatment

In dermatomycoses, the skin, nails, and hair are affected. The causative agents of dermatomycoses are *Trichophyton violaceum, Microsporum lanosum, Achorion schonlein,* different species of Epidermophyton, etc. Onichomycoses (fungal lesions of nails) are widely spreaded. Onichomycoses are caused by dermatophytes (most commonly by *Trichophyton rubrum*), Candida, and mild fungi (*Scopulariopsis brevicaulis, Aspergillus spp*., etc.). The fungi of the genus Candida and sometimes molds (causative agents of aspergillosis) are the most common pathogens among saprophytic fungi.

The most effective drugs for dermatomycoses treatment are *terbinafine (Lamisil), itraconazole, ketoconazole (Nizoral),* and *griseofulvin*. *Micospor, cyclopirox, amorolfine,* and *tioconazole* are used topically.

Griseofulvin is an antibiotic which is produced by mold-forming fungi *Penicillium nigricans*. The drug has narrow antifungal spectrum and is active against such causative agents of dermatomycoses as Trichophyton, Epidermophyton, Mikrosporum, and favus. Griseofulvin is ineffective against Candida and causative agents of deep mycoses. Mechanism of action is associated with violation of nucleic acid synthesis due to griseofulvin interaction with guanidine bases of RNA. The fungal resistance to griseofulvin does not develop in general. Griseofulvin is taken orally. The drug is readily absorbed from the gastrointestinal tract. Griseofulvin accumulates in the tissues, synthesizing keratin. Therefore, stratum corneum, nails, and hair become resistant to dermatomycetes. But in the upper epidermal layers, griseofulvin is determined only in 1–2 months after the start of therapy. Moreover, griseofulvin does not penetrate into the nail plates. Therefore, nail avulsion involves application of keratolytic agents. The daily dose of griseofulvin is divided into 4 intakes to provide the stable high drug concentration in the blood. Although a single drug intake of the daily dose is also possible. The duration of treatment with griseofulvin is 1–8 months. Also, liniment with griseofulvin is used topically.

The main routes of griseofulvin excretion from the body are kidneys and an intestine. A main part of the antibiotic dose undergoes the drug biotransformation in the liver.

The side effects of griseofulvin are headache, nausea, insomnia, disorientation, photodermatosis, fear, leukopenia, eosinophilia, etc. It is necessary to notice that nowadays the clinical use of griseofulvin is significantly restricted due to its cancerogenic property.

Terbinafine (Lamisil) is a derivative of N-methylnaphthalene. The drug affects ergosterol synthesis and formation of fungal membranes due to the influence upon the early steps of synthesis and violation of squalene accumulation. Lamisil exhibits the fungicidal effect. The spectrum of antifungal action includes dermatophytes and *Candida*. Terbinafine is taken orally. The drug is readily absorbed from the gastrointestinal tract and accumulates in the skin, subcutaneous fat, nail plates, hair follicles, and sebaceous glands. Terbinafine is metabolized in the liver and excreted through the kidneys. Lamisil cream is used topically twice a day.

The therapeutic indications for terbinafine are dermatomycosis of different localization and candidiasis. Most commonly the drug is used to treat onychomycosis and candidiasis of mucous membranes. The course of treatment lasts from 2 to 6 months. Lamisil is not recommended for pregnant women and for nursing mothers. The side effects of terbinafine are dyspepsia and allergic reactions. External drug use can cause itching and red skin.

Nitrofungin is a nitrophenol derivative. The drug is used topically as an alcoholic solution. Antifungal activity of nitrofungin is low.

The following drugs are also used topically for treatment of mycoses: *miconazole*, *clotrimazole*, preparations of undecylenic acid (ointments *"Zincundanum", "Mycoseptin", "Undecinum"*), and iodine preparations (*alcoholic iodine solution,* and *potassium iodide*).

Drugs for Candidiasis Treatment

Candidiasis most commonly affects mucous membranes of gastrointestinal tract, bronchi, sex organs, and skin. The main causative agent of candidiasis is *Candida albicans.*

Antibiotics *nystatin* and *levorin* exhibit fungiostatic and fungicidal effects. These drugs violate permeability of the fungal cell membrane. These drugs are characterized by low intestinal absorption. Nystatin and levorin are used orally to treat gastrointestinal candidiasis or to prevent candidiasis in patients treated by antibacterial drugs of broad spectrum. To treat candidiasis of oral cavity of sex organs, nystatin and levorin are used in solutions for syringing or in suppositories.

Toxicity of nystatin is very low. Its side effects are dyspepsia and allergic reactions. Levorin has a higher toxicity. But resistance of Candida to levorin develops more slowly. Levorin is also used in treatment of trichomoniasis and in therapy of patients with prostate adenoma.

Natamycin (pimafucin) is a polyene antibiotic with broad spectrum of antifungal action. Candida is especially highly sensitive to natamycin. Dermatophytes are less sensitive to natamycin. Pimafucin is used topically in treatment for candidiasis of the skin and mucous membranes. Suppositories with natamycin are used in treatment for vaginal candidiasis, and tablets – in treatment for intestinal candidiasis (drug is taken orally 4 times a day). To treat dermatomycoses, pimafucin is used in combination with griseofulvin. Toxicity of pimafucin is low. The side effects are dyspepsia and irritation and burning in case of local use.

Clotrimazole is imidazole derivative. It is a highly toxic agent which is used topically to treat candidiasis, resistant to polyene antibiotics.

Decaminum is bis-quaternary ammonium salt. It is a detergent with high surface activity. Decaminum violates permeability of fungal cytoplasmic membrane and due to this exhibits bactericidal, fungistatic, and fungicidal effects. The ointment with decaminum is used to treat fungal lesions of skin 1–2 times a day during

2–3 weeks. Decaminum is also effective in inflammatory lesions of the oral cavity, throat, and vagina.

Table 22 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Nystatinum	Orally 500 000 IU 3–4 times daily; for rectal or vaginal introduction 1 suppository 2 times daily; ointment for applying on the skin	Tablets 250 000 or 500 000 IU; suppositories 250 000 or 500 000 IU; ointment 1 % – 15.0 g
Amphotericinum B	Intravenously drop-by-drop 100–1 000 IU/kg (in 450 ml of 5 % glucose solution) 2–3 times per week; ointment for applying on injured parts of the skin	Vials with 50 000 IU of powder for injection; ointment 15.0 or 30.0 g (1 g contains 30 000 IU of amphotericinum B)
Ketoconazole	Orally 0.2–0.4 g once a day	Tablets 0.2 g
Itraconazole	Orally 0.1–0.2 g once a day	Capsules 0.1 g
Griseofulvinum	Orally 1 tablet 4 times daily; liniment for applying on injured parts of the skin	Tablets 0.125 g; liniment 2.5 % – 30.0 g
Fluconazole	Orally or intravenously drop-by-drop 0.05–0.4 g once a day	Capsules 0.05; 0.1; 0.2 g; vials 50; 100 or 200 ml of 0.2 % solution

Step 1. Tasks for Self-Control
Antiviral, Antiprotosoal, and Antifungal Drugs

1. A child was delivered to the hospital with punctated incrustation (white and yellowish spots) on the mucous tunics of cheeks, palate, and tongue caused by Candida albicans fungus. Which of the following drugs is used for treatment of the child?

A. Itraconazole.

B. Gentamicin sulfate.

C. Tetracycline hydrochloride.

D. Cefalexin.

E. Benzylpenicillin sodium.

2. A stomatologist diagnosed herpetic stomatitis. What is it necessary to prescribe for treatment in this case?

A. Sulfacylum-natrium.

B. Tetracycline.

C. Clotrimazole.

D. Acyclovir.

E. Itraconazole.

3. A patient suffers from candidiasis of mucous membranes of oral cavity. Choose the antibiotics group which is used for treatment of this patient.

A. Tetracyclines.

B. Polyene antibiotics.

C. Macrolides.

D. Aminoglycosides.

E. Penicillines.

4. Prescribe antiviral drug for patient suffering from surrounding herpes.

A. Lamivudine.

B. Ganciclovir.

C. Zidovudine.

D. Rimantadine.

E. Acyclovir.

5. A patient with amebic dysentery was prescribed a drug, which also inhibits the development of the erythrocyte forms of malaria plasmodium. What is it?

A. Quinine.

B. Emethine hydrochloride.

C. Chingaminum.

D. Erythromycin.

E. Tetracycline.

6. Systemic amebiasis with involvement of intestines, liver, and lungs was diagnosed in a 52-year-old patient. What drug should be prescribed?

A. Enteroseptol.

B. Metronidasole.

C. Quiniofone.

D. Chloroquine.

E. Tetracycline.

7. In order to prevent long-term effects of 4-day malaria a 42-year-old man was prescribed prymaquine. On the 3rd day from the begining of the treatment there appeared stomach and heart pains, dyspepsia, general cyanosis, hemoglobinuria. What could cause such side effects?

A. Potential activity with other preparations.

B. Delay preparation excretion with urine.

C. Reduced activity of microsomal liver enzymes.

D. Accumulation of the medication.

E. Genetic insufficiency of glucose-6-phosphate dehydrogenase.

8. Systemic amebiasis with involvement of intestines, liver, and lungs was diagnosed in a 52-year-old patient. What drug should be prescribed?

A. Enteroseptol.

B. Metronidasole.

C. Chloroquine.

D. Tetracycline.

E. Quiniofone.

9. Undergoing a metronidazole cure a patient drank a small amount of alcohol due to which a severe poisoning developed. What is the cause of the poisoning?

A. Disorder of kidney function.

B. Allergic reaction.

C. Acetaldehyde accumulation.

D. Cardiovascular collapse.

E. Neural disorders.

10. A female with dysentery is delivered to infectious unit. By means of laboratory investigations it is established that the causative agent of disease is *Entamoeba histolytica*. What drug should be prescribed to female?

A. Benzylpenicillin sodium salt.

B. Chingaminum.

C. Rifampicin.

D. Metronidazole.

E. Isoniazid.

11. Drug A. is prescribed to patient with ulcer disease of stomach. It is known that drug A. suppresses the growth and reproduction of *H. pylori*. Indicate this drug.

A. Metronidazole.

B. Glauvent.

C. Prazosin.

D. Corglycon.

E. Furosemide.

12. Indicate the drug which should not be used with ethyl alcohol, because this drug inhibits ethanol metabolism.

A. Aminazine.

B. Metronidazole.

C. Clophelinum.

D. Diazepam.

E. Reserpine.

13. A 30-year-old patient complains of having abdominal pain and diarrhoea for five days; body temperature rises up to 37.5 ^{0}C along with chills. The day before a patient had been in a forest and drunk from an open water reservoir. Labotatory analyses enabled to make the following diagnosis: amebic dysentery. What is the drug of choice for its treatment?

A. Levomycetin.

B. Phthalazolum.

C. Metronidazole.

D. Emetine hydrochloride.

E. Furazolidone.

ANTHELMINTIC DRUGS

More than 250 species of worms can parasitize in a human body. The worms cause an enormous damage for the host organism due to the release of toxins and mechanical damage of the internal organs. Helminthiases can cause anemia, allergic reactions, disordes of the central nervous system activity, gastrointestinal distress, functional disturbances of the liver, lungs, eyes, blood and lymphatic vessels, etc. The incidence of worm infections is quite high.

Depending on localization of worms in the human organism, there are intestinal and extraintestinal helminthiases. Depending on the types of worms, which cause the disease, helminthiases are divided into nematodiasis (causative agents are roundworms or nematodes), cestodiasis (causative agents are flatworms or cestodes), and trematodiasis (causative agents are flukes or trematodes).

Drugs for Intestinal Helminthiasis Treatment

Drugs for Intestinal Nematodiasis Treatment

The following drugs are used to treat intestinal nematodiasis: *mebendazole, albendazole, levamisole, medamin, naftamon, piperazine, pervinium pamoate,* and *pyrantel pamoate*.

Mebendazole (Vermox) is a benzimidazole derivative. The drug has a broad spectrum of anthelmintic action which includes main types of roundworms: *Ascaris lumbricoides* (causative agent of ascariasis), *Enterobius vermicularis* (enterobiasis), *Trichocephalus trichiurus* (trichocephaliasis), *Ancylostoma duodenale* (ancylostomiasis), and *Strongyloides stercoralis* (strongyloidiasis). Mebendazole is active against infections, caused by cestodes *Taeniarhynchus saginatus* (bovine tapeworm), *Hymenolepis nana* (dwarf tapeworm), and *Taenia solium* (pork tapeworm). Vermox affects both worms and their eggs.

The mechanism of mebendazole action is associated with violation of glucose absorption by worms that results in disturbances of energy metabolism. At the same time, the violation of glucose absorption by mammalian cells is not observed. The inhibition of

motor activity and death of helminths develop gradually. The excretion of dead parasites with feces is observed during several days.

Mebendazole is taken orally during or after a meal. Gastrointestinal absorption of mebendazole is low (not more than 10 %). The absorbed part of the drug undergoes hepatic metabolism and is excreted by the kidneys within 1–2 days. For better absorption, an intake of mebendazole suspension in sunflower oil is recommended. The treatment with mebendazole does not require a special diet. The single mebendazole intake is used in case of invasion by *Ascaris lumbricoides* or *Enterobius vermicularis*. Repeated intake of the drug is recommended in two weeks. To treat other helminthiases, the course of treatment with mebendazole varies depending on the type of helminth.

The therapeutic indications for mebendazole are intestinal nematodiasis (ascariasis, enterobiasis, ankylostomiasis, trichocephaliasis, and strongyloidiasis), intestinal cestodiasis (teniasis, teniarinchiasis, and hymenolepiasis), extraintestinal nematodiasis (filariasis and trichinelliasis), and extraintestinal cestodiasis (cysticercosis and echinococcosis).

Albendazole (Vormil) is effective in intestinal nematodiasis, cysticercosis, and echinococcosis. Vormil also affects the eggs of *Ascaris lumbricoides*, *Ancylostoma duodenale*, and *Trichocephalus trichiurus* (whipworm). The drug violates glucose utilization by helminths. Taken orally, albendazole is easily absorbed from the gastrointestinal tract and metabolized in the liver. The drug metabolites are excreted mainly by the kidneys. The side effects of albendazole are headache, diarrhea, dizziness, and insomnia. Prolonged intake of albendazole can cause leukopenia, vomiting, skin rash, abdominal pain, and alopecia.

Pyrantel pamoate is a pyrimidine derivative. The drug is used at invasion by roundworms. Pyrantel violates neuro-muscular transmission due to cholinesterase inhibition. It results in spastic paralysis of helminths. Pyrantel is taken orally. The degree of intestinal drug absorption is about 50 %. The main route of excretion

is the intestine. The therapeutic indications for pyrantel are ascariasis, enterobiasis, ancylostomiasis, and trichostrongyliasis. Side effects of pyrantel are dyspepsia, loss of appetite, and headache.

Levamisole (decaris) is commonly used in ascariasis treatment. The drug causes depolarization of helminth muscular membranes that results in muscular paralysis. Besides, levamisole inhibits the activity of fumaratereductase and violates metabolism of the helminths. Simple drug intake provides the full dehelminthization in 90–100 % of patients with ascariasis. Levamisole activity is lower in ancylostomiasis and strongyloidiasis. Levamisole effects positively in patients with extraintestinal helmintiasis, for instance with filariasis.

The side effects of levamisole are abdominal pain, nausea, vomiting, and headache.

Levamisole also has immunomodulatory effect. The drug normalizes function of macrophages and T-lymphocytes in patients with immunodeficiency. The course of treatment with levamisole lasts from 2–3 weeks up to a year. Prolonged therapy with levamisole can be aggreveted by a lot of serious side effects: insomnia, disorders of taste and smell, skin rash, and agranulocytosis.

Piperazine adipate is widely used to treat ascariasis and enterobiasis. Pyperazine paralyzes the neuromuscular systems of helminths that prevents their movement through the intestine and penetration into the bile ducts. Also, pyperazine stimulates the intestinal peristalsis that provides favorable conditions for evacuation of helminths from the intestine. The drug is readily absorbed from the intestine, its metabolites are excreted with the urine. The treatment with pyperasine does not require a special diet and intake of laxative drugs. An efficacy of pyperazine in ascariasis is 90–100 %. Pyperazine is a low toxic drug. Its side effects are dyspepsia and headache.

Naftamon is a monoquaternary ammonium compound. The drug is highly effective in ascariasis, enterobiasis, ankylostomiasis, and trichostrongyliasis. Mechanism of action is associated with

inhibition of neuromuscular transmission of helminths. Naftamon is characterized by low ability to absorb from gastrointestinal tract and laxative activity. A very bitter taste of naftamon is the cause of nausea and vomiting. Naftamon is prescribed for oral intake for 1–2 hours before a meal.

Pyrvinium pamoate is mainly used to treat enterobiasis and strongyloidiasis. The drug inhibits aerobic respiration of helminths and violates the utilization of exogenic glucose. The absorption from gastrointestinal tract is low. Pervinium seldom causes the side effects.

Drugs for Intestinal Cestodiasis Treatment

The drugs to treat intestinal cestodiasis are *praziquantel, niclosamide (phenasalum), extract of male fern, pumpkin seeds*, etc.

Niclosamide (phenasalum) is active against *Taenia solium, Taeniarincus saginatus, Diphyllobothrium latum*, etc. The drug inhibits phosphorylation in mitochondria of cestodes, utilization of oxigen and glucose by helminths, and paralyzes their neuromuscular system. Besides, niclosamide decreases the resistance of helminths to proteolytic enzymes of the gastrointestinal tract that provokes degradation of the coating tissues of helminths. The treatment with niclosamide requires a specific patient preparation – carbohydrate diet because proteins bind to drug and inactivate it. Overnight, the patient drinks only tea and fruit juice and gets an enema. Niclosamide is taken in the morning on an empty stomach. Laxative drugs are given only in case of teniasis (to prevent cysticercosis). Niclosamide is readily absorbed from the gastrointestinal tract. About 25–30 % of the drug is excreted from the body in urine, another part – in feces. Side effects of niclosamide are nausea, vomiting, and abdominal pain.

Praziquantel (biltricide) is highly effective drug to treat intestinal cestodiasis (teniasis, diphyllobothriasis, teniarinchiasis, and hymenolepiasis), extraintestinal trematodiasis, and cysticercosis. Praziquantel increases permeability of calcium in helminthic cell

membranes. Calcium entrance causes a short-time increase of muscular activity which is replaced by spastic paralysis of helminths. Praziquantel is readily absorbed from the gastrointestinal tract, undergoes fast hepatic metabolism, and is being excreted by the kidneys. Side effects of praziquantel are dyspepsia, headache, and skin rash. The drug is contraindicated in first trimester of pregnancy and for nursing mothers.

The *extract of the male fern* is obtained from the rhizome of this plant. The extract contains dezaspidin, dezaspidiol, and other derivatives of phloroglucinol. The taken orally drug is practically not absorbed from the gastrointestinal tract. However, the presence of fats can increase the gastrointestinal absorption of the extract that results in poisoning. The extract of the male fern causes the muscular paralysis in helminths, therefore, parasites can not attach to the intestinal wall. The extract of the male fern is used to treat teniasis, diphyllobothriasis, teniarinchiasis, and hymenolepiasis. Due to high toxicity, the treatment by the extract of the male fern is carried out according to certain regimen and only in the hospital. Two days before treatment, a special diet with easily digestible meatless products is prescribed to a patient. In the evening before the drug intake, a patient drinks a cup of tea with rusk. The laxative drug is prescribed for the night. In the morning, the patient receives the cleansing enema and takes the drug (required number of capsules within 30 minutes). The capsules are washed down by a solution of sodium hydrocarbonate. It is necessary for pyloric relaxation and increase of drug evacuation rate from the stomach into the intestine. After 1–1.5 hours, the patient receives the laxative drug. If laxative effect does not develop in 3 hours, the patient receives the cleansing enema. Side effects of the extract of the male fern are headache, vomiting, diarrhea, convulsions, paralysis, respiratory depression, atrophy of the optic nerve, heart disorders, and collapse. Due to high toxicity, the extract of the male fern is used seldom.

Mebendazole may be used to treat some cases of cysticercosis.

Drugs for Intestinal Trematodiasis Treatment

Ethylene tetrachloride and *praziquantel* are used to treat metagonimosis (caused by *Metagonimus yokogawai*).

Ethylene tetrachloride is taken orally. The drug absorption from the gastrointestinal tract is low. The special fat-free and carbohydrate-rich diet should bt used during 1–2 days to prepare a patient to treatment. Also, alcohol is contraindicated during this time. In 15–20 minutes after ethylene tetrachloride intake, the patient receives saline laxative drug. Ethylene tetrachloride is also effective in ancylostomiasis.

Drugs for Extraintestinal Helminthiasis Treatment

Drugs for Extraintestinal Nematodiasis Treatment

Filariasis is the most common extraintestinal nematodiasis. There are several causative agents of filariasis: *Wunchereria Bancrofti* and *Brugia malayi* affect the lymphatic system; *Loa Loa* parasitizes in the subcutaneous fat; *Onchocerca volvulus* parasitizes in the subcutaneous fat and in the eyes. Other widely spread extraintestinal nematodiasis is trichinelliasis at which *Trichinella spiralis* affects the skeletal muscles (larval stage) and the intestine (mature stage).

To treat extraintestinal nematodiasis, *diethylcarbamazine (ditrazinum)* and *ivermectin* are used.

Diethylcarbamazine is an effective drug for filariasis treatment (the highest activity against microfilariae). The drug is easily absorbed from the gastrointestinal tract, it undergoes partial biotransformation and is excreted in the urine within 2 days. Ditrazinum inhibits the ability of microfilariae to resist phagocytosis. Ditrazinum exhibits a nematicidal effect. However, diethylcarbamazine provides the marked therapeutic effect only at early stages of the disease. The side effects of diethylcarbamazine are headache, weakness, nausea, and vomiting. These complications are caused by toxic influence of decomposition products of microfilariae and rapidly disappear.

Ivermectin is highly active againt microfilariae and Strongyloides stercolaris, but not active against macrofilariae. Ivermectin is semisynthetic macrocyclic lactone compound. The drug is taken orally. Therapeutic effect develops after a single intake. Ivermectin causes the flaccid paralysis of helminths due to inhibition of GABA. The highest drug activity develops when treating onchocercosis (blinding filarial disease or river blindness). The side effects of ivermectin are fever, drowsiness, dizziness, headache, bronchospasm, etc.

There are no effective drugs for trichinelliasis treatment. Certain positive effect in this case is possible for *mebendazole*.

Drugs for Extraintestinal Trematodiasis Treatment

Schistosomiasis is the most common extraintestinal trematodiasis. The causative agents of schistosomiasis are *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. These parazites affect the blood vessels that results in disorders of internal organs (intestine, liver, lungs, spleen, urogenital system, etc.).

The most effective drug for schistosomiasis treatment is *praziquantel (Biltricide)*. The drug is also effective in other extraintestinal trematodoses:

– opisthorchiasis (causative agent is *Opisthorchis felineus* which affects the liver and pancreas);

– clonorchiosis (*Clonorchis sinensis* parasitizes also in the liver and pancreas);

– paragonimiasis (*Paragonimus Westermani* affects the brain, lungs, and lymphatic system);

– fascioliasis (*Fasciola hepatica* parasitizes in the liver and gallbladder).

Besides, praziquantel is used to treat metagonimiasis. The pharmacological characteristics of praziquantel is given above.

Antimony sodium tartrate is a drug containing antimony. The drug is administered intravenously, slowly, daily during 20 days. Antimony sodium destroys helminth larvae which are located in

eggs. Also, the drug interacts with thiol groups of enzymes, and due to this, inhibits the vital functions of helminths. Antimony sodium tartrate is a toxic agent and commonly causes side effects. The drug may cause phlebitis. Accidental subcutaneous administration of its solution causes sharp pain and tissue oedema. Weakness, headache, extrasystoles, metallic taste, nausea, muscular and joint pain, hypotension, insomnia, skin rash, cough, chest pain, and anaphylaxis are also possible side effects of antimony sodium tartrate. The drug is contraindicated in patients with diseases of heart, liver, and kidneys, in pregnant women, and during menses. In case of drug overdose, unithiol is used as an antidote.

Chloxilum is an effective agent in treatment for opisthorchiasis and fascioliasis in which helminths affect the liver, bile ducts, and pancreas. Chloxilum reduces the helminth resistance to the action of helminth proteolytic enzymes that results in death of helminths. The drug is taken orally. Patient preparation to treatment lasts 1–2 days, and duration of therapy with chloxilum is 2 days. Within this time, a patient adheres to the fat-free diet and excludes alcohol. Therapeutic efficacy of chloxilum is 35–40 %. In significant number of patients, only reduction in invasion severity is observed. The helminth eggs can be released from the body during 3 months after treatment. Taken orally chloxilum is slowly and incompletely absorbed from the intestine. A main part of the taken dose is excreted from the intestine in feces during the first day. Another part of the drug, which has reached the systemic blood circulation, is accumulated in the body and excreted within 6–28 days. The side effects of chloxilum are headache, light inebriation, drowsiness, pain in the liver and heart, and allergic reactions. Chloxilum is contraindicated in patients with diseases of heart, liver, and in pregnant women.

Bithionol and emetine hydrochloride are used for treatment of fascioliasis.

Bithionol is a drug of choice for paragonimiasis treatment. Typical side effect of this drug is diarrhea.

Drugs for Extraintestinal Cestodiasis Treatment

In extraintestinal cestodiasis treatment, some success has been recently achieved. Thus, therapy with *mebendazole* and *albendazole* exhibits positive results in treatment for echinococcosis and cysticercosis. *Praziquantel* is used to treat cysticercosis, but the drug is ineffective when helminths depoint in the spinal cord and into the cerebral ventricles.

Table 23 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Mebendazolum	Orally 0.1 g once (only for treatment of enterobiasis) or 0.1–0.4 g 2–3 times a day	Tablets 0.1 g
Piperazini adipinas	Orally 1.5–2.0 g 2 times a day	Tablets 0.2 or 0.5 g
Phenasalum	Orally 2.0 g	Tablets 0.25 g
Ditrazini citras	Orally 0.002 g/kg 3 times a day	Tablets 0.05 or 0.1 g
Praziquantel	Orally 0.025–0.04 g/kg	Tablets 0.6 g
Chloxilum	Orally 0.06 g/kg	Powder

ANTITUMORAL DRUGS

Antitumoral drugs are agents with different chemical structure which are able to inhibit the division of malignant cells in various stages of cell cycle. These drugs are used in chemotherapy for different oncological diseases. According to medical statistics, malignant solid tumors and blood diseases rank second among the causes of human death.

Nowadays, about 200 antitumoral drugs are used in oncology. But drugs which are fatally toxic for malignant cells and simultaneously safe for normal body cells are still not developed. Therefore, one of the most important principles for modern

chemotherapy is a simultaneous use of several drugs with different chemical structures and mechanisms of action. This enables to increase antitumoral activity and to reduce the toxicity of the drugs.

Classification of antitumoral drugs is as follows.

1. Cytotoxic drugs.

1.1. Alkylating agents:

– chloroethylamines: *embichin (chlormethine), sarcolysin (melphalan), dopanum (chlorethylaminouracil, uramustine), prospidine, chlorbutinum (chlorambucil),* and *cyclophosphan (cyclophosphamide)*;

– ethylenimines: *thiodipine* and *thiophosphamide (ThioTEPA),* ;

– methanesulphonic acid derivatives: *myelobromol* and *myelosanum (busulfan)*;

– nitrosourea derivatives: *nitrosomethylurea, carmustine,* and *lomustine.*

1.2. Antimetabolites:

– folic acid antagonists: *methotrexate*;

– purine antagonists: *mercaptopurine*;

– pyrimidine antagonists: *phthoruracilum (fluorouracil), cytarabine,* and *ftorafur (tegafur).*

1.3. Cytotoxic antibiotics: *dactinomycin, rubomycin, carminomycin, olivomycin, bruneomycin, bleomycin, epirubicin,* and *mitomycin.*

1.4. Cytotoxic drugs of plant origin:

– Vinca rosea alkaloids: *vinblastine* and *vincristine*;

– taxanes (alkaloids of yew-free): *paclitaxel (taxol), docetaxel,* and *taxotere*;

– podophyllotoxin (obteined from Podophyllum peltatum): *etoposide, teniposide,* and *podophylline*;

– alkaloids of Colchicum autumnale: *colchamine* and *colchicine*.

1.5. Other synthetic cytotoxic drugs: *cisplatin, carboplatin, dacarbazine,* and *procarbazine*.

2. Hormones and their antagonists:

– androgens: *testosterone propionate, tetrasterone, testenate,* and *medrotestrone propionate*;
– antiandrogens: *flutamide* and *cyproterone (androcur)*;
– estrogens: *fosfestrol, diethylstilbestrol,* and *ethinyl estradiol*;
– antiestrogens: *tamoxifen* and *toremifene*;
– progestins: *oxyprogesterone capronate* and *medroxy-progesterone acetate*;
– analogues of gonadotropin-releasing hormone: *goserelin* and *leuprorelin*;
– inhibitors of aromatase: *aminoglutethimide* and *letrozole*.
– glucocorticoids: *prednisolone* and *dexamethasone*.

3. Enzymes: *L-asparaginase*.
4. Cytokins:
– interferons: *α-interferon*;
– interleukins: *aldesleukin*.
5. Monoclonal antibodies: *herceptin*.
6. Tyrosine kinase inhibitors: *imatinib, gefitinib,* and *erlotinib*.

Most antitumoral drugs cause multiple side effects which restrict their clinical use. To prevent or reduce these side effects, the following drugs are used.

1. Drugs stimulating hemopoiesis (colony-stimulating factors).
1.1. Drugs stimulating leucopoiesis: *molgramostim (Leucomax)* and *filgrastim.*
1.2. Drugs stimulating erythropoiesis: erythropoietins (*epoetin alfa* and *epoetin beta*).
2. Antiemetic drugs: *ondansetron, tropisetron,* and *metoclopramide.*
3. Immunomodulators: *interferons, interleukins, thymus preparations,* and *levamisole.*
4. Drugs which inhibit manifestations of carcinoid syndrome associated with malignant neuroendocrine tumors: *octreotide.*

5. Drugs which prevent osteoporosis associated with tumor metastasis spread to bones: bisphosphonates (*pamidronate, clodronate,* and *zoledronate*).

Alkylating Drugs

Alkylating drugs include cytotoxic agents of different chemical strucrure with identical mechanism of action. It is believed that radicals of alkylating drugs form covalent bonds with different molecules of the cell. The bonds with guanine of DNA are the most important. As a result, the cross-linking of DNA strands occurs. DNA double helix loses its ability to diverge, gene mutations occur, and replication is violated.

Embichin (chlormethine) is the first drug of subgroup of chloroethylamine. Like most drugs of this group, embochin is used to treat hemoblastoses (chronic leukemia, lymphosarcoma, lymphogranulomatosis, reticulosarcoma, etc.).

Sarcolysin (melphalan) is chloroethylamine derivative. The drug is used in lymphosarcoma, reticulosarcoma, multiple myeloma, and some solid tumors (testicular seminoma, and Ewing sarcoma). In testicular seminoma, sarcolysin is effective even in the presence of metastases. Sarcolysin is administered parenterally or taken orally.

Cyclophosphan (cyclophosphamide) is the most effective drug within chloroethylamine derivatives. It is a prodrug which is transformed in the human body into the metabolites with antitumoral activity. Cyclophosphan is used to treat hemoblastoses, multiple myeloma, testicular cancer, breast cancer, and small-cell lung cancer (small-cell carcinoma). Cyclophosphan causes a long-term remission in patients with lymphoid leukemia. The drug is administered parenterally and taken orally.

Dopanum (uramustine) and *chlorbutinum (chlorambucil)* are also used to treat hemoblastoses. Both drugs are taken orally.

Prospidine is chlorethylamine derivative which is used in laryngeal cancer treatment.

Thiophosphamide (ThioTEPA) is ethylenimine derivative which is used in treatment for hemoblastoses (chronic leukemia,

lymphogranulomatosis, lymphosarcoma, reticulosarcoma) and solid tumors (testicular cancer and breast cancer).

Methanesulphonic acid derivatives *myelosanum (busulfan)* and *myelobromol* are used in exacerbation of chronic myeloid leukemia. Both drugs are taken orally.

Drugs – nitrosourea derivatives are *nitrosomethylurea*, *lomustine*, and *carmustine*. Nitrosomethylurea is effective at small-cell carcinoma and lymphogranulomatosis. Other drugs are used in treatment for brain cancer, colon and rectal carcer, Hodgkin's disease, and other lymphomas. Another representative of nitrosourea derivatives is *fotemustine*. The drug is used to treat malignant melanoma and primary brain tumors.

Dacarbazine and *procarbazine* are cytotoxic agents – derivatives of triazenes which are used in melanoma treatment.

Cisplatin is platinum compound which is used to treat testicular tumors, ovary cancer, bladder cancer, squamous head and neck cancer, endometrial cancer, lymphomas, and non-small cell lung cancer. Like alkylating drugs, cisplatin chemically interact with DNA that results in violation of DNA function.

All alkylating drugs are characterized by high toxicity. Therapy by these drugs is accompanied by nausea, vomiting, hemopoiesis depression (anemia, thrombocytopenia, and neutropenia), ulceration of gastrointestinal tract and bladder, etc. Intravenous administration of alkylating drugs can cause thromoflebitis. Amenorea, impotention, and hair loss are also possible. At present, cytokins (filgrastim and molgramostim), erythropoietin, and some interleukins are used to stimulate hemopoiesis. Antibiotics are used to prevent and treat various infections.

Antimetabolites

Antimetabolites are structural analogues of natural metabolites: folic acid, purines, and pyrimidines. The mechanism of their action is based on the drug ability to compete with natural metabolites and replace them in the body compounds. Since antimetabolites cannot fulfil the normal physiological functions, their incorporation in

molecules of nucleic acid blocks its normal synthesis. Antimetabolites are active only against dividing malignant cells. These drugs do not influence dormant stem cells of tumors.

Folic acid antagonist *methotrexate* and purine antagonist *mercaptopurine* are mainly used in acute lymphoblastic leukemia treatment. Methotrexate has higher activity in children, but mercaptopurine – in adult patients. Besides, both drugs are used in uterine horionepithelioma. Methotrexate is also used in chemotherapy for such solid tumors as breast cancer. Both drugs are taken orally, and methotrexate is administered parenterally.

Phthoruracilum (fluorouracil) is a pyrimidine antagonist. The drug is used in therapy of solid tumors: cancer of stomach, pancreas, breast, and colon. Fluorouracil causes temporal tumor regression in some patients. Fluorouracil is administered intravenously. For peroral intake, capecitabine was created. It is a prodrug which, under the influence of thymidine phosphorylase, is transformed into fluorouracil.

Ftorafur (tegafur) is a less toxic drug than fluorouracil. The drug is used in breast cancer, cancer of stomach, colon, and rectum.

Cytarabine and *thioguanine* are used in chemotherapy for acute myeloid and lymphoid leukemia.

Antimetabolites are highly toxic drugs. Their side effects are nausea, vomiting, inhibition of hemopoiesis, lesions of gastrointestinal tract, hair loss, etc. Only mercaptopurine and thioguanine are relatively well tolerated by patients.

Cytotoxic Antibiotics

Cytotoxic antibiotics are produced by different species of Streptomyces and Actinomycetes. These drugs have different chemical structure. Mechanism of action is associated with inhibition of synthesis and function of nucleic acids that results in suppression of cell division.

Dactinomycin is produced by actinomycetes. The drug is used in chemotherapy for horionepitelioma, Wilms' tumor

(nephroblastoma) of children, and lymphogranulomatosis. Dactinomycin is administered intravenously or into the body cavities.

Olivomycin is a derivative of aureolic acid which is produced by actinomycetes. Olivomycin is used in the treatment for seminoma, teratoblastoma, embryonal carcinoma, lymphoepithelioma, reticulosarcoma, and melanoma. The drug is administered intravenously or applied topically in ointments.

Rubomycin, doxorubicin (Adriamycin), carminomycin are anthracycline antitumor antibiotics. These drugs are used in the treatment for sarcomas of mesenchymal origin. Also, doxorubicin is used in bone sarcoma, breast, lungs, bladder, thyroid, and ovarian cancer, etc. Rubomycin is used in treatment for acute leukemia, reticulosarcoma, and uterine horionepithelioma.

Bleomycin is cytotoxic glycopeptide antibiotic produced by *Streptomyces verticillus*. The drug is used in treatment for squamous cell carcinoma of the oral mucosa, tongue, tonsil, skin, and uterus. Also, bleomycin is used in lymphogranulomatosis and penile cancer.

Bruneomycin is used in treatment for lymphogranulomatosis, reticulo- and lymphosarcoma, and chronic lymphocytic leukemia.

Cytotoxic antibiotics may be combined with other antitumoral drugs, except alkylating drugs and antimetabolites.

It is necessary to notice that all cytotoxic antibiotics have also antibacterial activity, but it has no practical value.

Cytotoxic antibiotics are drugs with high toxicity. Chemotherapy with them is accompanied by numerous side effects: appetite loss, nausea, vomiting, diarrhea, candidiasis, inhibition of hemopoiesis, hair loss, fever, hypotension, cardiotoxicity, allergic reactions, and anaphylactic shock.

Antitumoral Drugs of Plant Origin

Vinblastine and *vincristine* are alkaloids of *Vinca rosea*. Their mechanism of action is associated with metaphase-blockage mitosis due to disruption in formation and function of the microtubule spindle. It results in violation of DNA divergence to the

poles of the cell, the following degradation of DNA strands, and cell death.

Both drugs are used in the treatment for hemoblastoses (acute leukemia, reticulo- and lymphosarcoma), lymphogranulomatosis, breast cancer, neuroblastoma, etc. *Vinca rosea* alkaloids are commonly combined with other antitumoral drugs. Both drugs are administered intravenously. Their side effects are inhibition of hemopoiesis, nephrotoxicity, neurological disturbances (ataxia, violation of neuro-muscular transmission), alopecia, jaundice, etc.

Yew-tree (*Taxus*) preparations are *paclitaxel (taxol)* and *docetaxel (Taxotere).* These drugs exhibit antimitotic activity due to interaction with tubulin. Taxones are used in the treatment for breast and ovarian cancer, small cell lung cancer, and epithelial tumors of the head and neck. The side effects of taxones are nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, hypotension, etc.

Podophyllum peltatum (mayapple) preparations are *etoposide*, *teniposide,* and *podophylline.* These drugs are used in the treatment for laryngeal and bladder papillomatosis, small cell lung cancer, Ewing's sarcoma, etc.

Colchamine and *colchicine* are alkaloids of *Colchicum autumnale* and *Colchicum speciosum.* Colchamine is used topically in ointment in the treatment for skin cancer, esophagus, and stomach cancer (in the combination with sarcolysin). Colchamine kills malignant cells practically without damage of normal epithelial cells. Colchamine can cause skin rashes. After removing necrotic tissue, wounds may be healed with good cosmetic result.

Besides, some plant preparations are used as antitumoral agents: befungin, drugs of celandine, calendula, wild poppy, plantain, etc.

Enzymes

L-asparaginase is enzyme which is used in the treatment for acute lymphoblastic leukemia and lymphosarcoma. This enzyme distroys L-asparagine. L-asparagine is amino acid which is required for the synthesis of proteins, RNA, and DNA. Side effects

of L-asparaginase are neuro-, nephro- and hepatotoxicity, and affection of pancreas.

Hormonal Drugs and Their Analogues

This group includes male and female sex hormones and their antagonists, and also glucocorticoids which play complementary role. Sex hormones are used in the treatment for malignant neoplasms of ovaries, uterus, prostate, and breast. There are evidences that under the influence of sex hormones, malignant cells do not die because hormonal drugs only slow down their division and metastasis.

As a rule, chemotherapy with sex hormones is combined with surgical and radiation treatments.

Androgens (*testosterone propionate, testenate, tetrasterone, medrotestrone propionate*) are used to treat breast cancer in women with menstrual cycle and in the first 5 years after menopause. In these cases, androgens inhibit production of estrogens. The use of high androgen doses is accompanied by virilization (excess facial and body hair, baldness, acne, deepening of the voice, increased muscularity), dizziness, nausea, etc.

Antiandrogens include such drugs as *flutamide* and *cyproterone (androcur)*. Their mechanism of action is associated with the inhibition of transport and binding of dihydrotestosterone with receptors in the prostatic cells. It results in slowing down tumoral cell growth in the prostate. Both drugs are taken orally. Antiandrogens exhibit high efficacy in prostate cancer and cause prolonged remission in the majority of patients. The drugs are well tolerated by patients. Prolonged anti-androgen therapy may be accompanied by the development of gynecomastia, but it does not affect sexual function.

Estrogens (*fosfestrol, diethylstilbestrol, ethinylestradiol*) are used to treat breast cancer in women with menopause which lasts more than 5 years. In these patients, estrogens inhibit the production of pituitary gonadotropins which indirectly stimulate the growth of tumoral cells.

Besides, estrogens are used in the treatment for prostate cancer. In this case, estrogens inhibit the function of natural androgens. One of the drugs for prostate cancer treatment is fosfestrol (sodium salt of diphosphoric ether of diethylstilbestrol). Under the influence of acid phosphatase of tumoral cells, fosfestrol is transformed into diethylstilbestrol. Fosfestrol is taken orally or administered intravenously. Fosfestrol is characterized by fast efficacy development and low toxicity in contrast to diethylstilbestrol. The use of estrogens in males can cause feminization, dyspepsia, itchy skin, and hemorrhagic rash. In 1–2 years of estrogen use, malignant cells lose the sensitivity to these agents.

Antiestrogens (*tamoxifen, toremifene*) bind to estrogen receptors of neoplastic cells of the breast and prevent estrogen-induced tumor growth. Antiestrogens are used to treat estrogen-induced breast cancer, especially in postmenopausal women. The side effects of these drugs are vaginal hemorrhage, redness of the skin, vomiting, dermatitis, etc.

At present, drugs inhibiting the synthesis of androgens are introduced in the medical practice. These drugs are aromatase inhibitors. In postmenopausal period, estrogens are synthesized from androgens which are produced by adrenal cortex. This process is regulated by enzyme aromatase. Inhibition of aromatase results in violation of estrogen synthesis.

Aromatase inhibitors are such drugs as *letrozole (Femara), aminoglutethimide (Cytadren), anastrozole (Arimidex),* etc. Aromatase inhibitors are used to treat breast cancer and ovarian cancer in postmenopausal women and gynecomastia in men. Their side effects are headache, dyspepsia, skin rash, weakness, vaginal bleeding, etc.

Progestins (*oxyprogesterone caproate, medroxy-progesterone acetate*) are used to treat uterine cancer. Progestins cause the cancer regression in significant number of patients.

Analogues of gonadotropin-releasing hormone (*goserelin, leuprorelin*) also exhibit the antitumoral activity. In case of continuous use, these drugs reduce the secretion of gonadotropins by

the anterior pituitary and exhibit therapeutic effect in patients with prostate cancer.

Glucocorticoids and preparations of *adrenocorticotropin* are commonly used to treat acute leukemia in children, chronic lymphocytic leukemia, lymphogranulomatosis, and lymphosarcoma.

Cytokines

Cytokines include interferons and interleukins.

Recombinant human interferon α is interferon which is used in the complex treatment for some tumors. The drug activates macrophages, T-lymphocytes, and T-killer cells. Recombinant human interferon α is effective in multiple myeloma, Kaposi's sarcoma, renal cell carcinoma, etc. The drug is administered parenterally. Side effects of this drug are headache, fever, myalgia, arthralgia, dyspepsia, blood dyscrasias, thyroid dysfunction, etc.

Interleukin-2 (proleukin) stimulates proliferation and differentiation of T-helpers and cytotoxic T-lymphocytes, activates macrophages, stimulates proliferation of B-lymphocytes. Proleukin is derived by genetic engineering. The drug is administered parenterally. Side effects are hypotension, pulmonary oedema, inhibition of hematopoiesis, nephrotoxicity, lesions of the central nervous system, and allergic reactions.

Monoclonal Antibodies

Monoclonal antibodies include *trastuzumab (Herceptin)* and *rituximab (Mabthera)*. These drugs are produced by genetic engineering. Both drugs are administered intravenously. Monoclonal antibodies are used in complex chemotherapy for some oncological diseases.

Herceptin is an antibody against antigenic HER2 (human epidermal growth factor receptor 2) of the breast malignant cells that results in cytotoxic effect. Overexpression of these receptors leads to proliferation and malignant transformation of the cells. Overexpression of HER2 protein is observed in 20–30 % of patients

with breast cancer. Therapeutic indication for trastuzumab is metastatic breast cancer with HER2 protein overexpression.

Rituximab interacts with protein CD20 which is an antigen located on the membranes of B-cells of non-Hodgkin's lymphomas.

Bevacizumab (Avastin) is a monoclonal antibody preparation which blocks the vascular endothelial growth factor. The drug inhibits the growth of tumor vessels that violates its blood supply and slows down the tumoral growth. Avastin is administered intravenously. Bevacizumab is used in complex chemotherapy for colorectal cancer.

The side effects of monoclonal antibodies are fever, nausea, vomiting, skin rash, headache, hypo- or hypertension, nephrotoxicity, oedemas, bronchospasms, a cough, lymphopenia, leukopenia, etc.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors include *imatinib, gefitinib,* and *erlotinib*. It is a new group of antitumoral drugs. Tyrosine kinase is an important functional element of membrane receptors – growth factors of thrombocytes, epithelium, stem cells, vascular endothelium, nerves, etc. Besides, there are tyrosine kinases of the cytoplasmic and nuclear localization. Tyrosine kinase regulates the growth and differentiation of cells and their apoptosis.

The first representative of this group is *imatinib*. The drug blocks tyrosine kinase of the receptors for platelet-derived growth factor, stem cell factor, and cytoplasmic tyrosine kinase. Imatinib is used to treat chronic myelogenous leukemia and gastrointestinal stromal tumors. The drug is taken orally. Side effects of imatinib are nausea, vomiting, neutropenia, skin rash, etc.

Gefitinib blocks tyrosine kinase of the receptor for epidermal growth factor. The drug is used to treat non-small cell lung cancer and head cancer.

Erlotinib blocks several receptor tyrosine kinases, and it is used to treat non-small cell lung cancer.

Sunitinib is used to treat gastrointestinal stromal tumors and a clear-cell subtype of renal cell carcinoma.

Table 24 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Cyclophosphanum	Orally, intramuscularly or intravenously 0.2 g once a day; 0.4 g once every 2 days	Coated tablets 0.05 g; ampoules 0.1 or 0.2 g of powder for solution
Chlorbutinum	Orally 0.002–0.01 g once a day	Tablets 0.002 or 0.005 g
Myelosanum	Orally 0.002–0.01 g once a day	Tablets 0.002 g
Mercaptopurinum	Orally 0.001–0.001 25 g/kg once a day	Tablets 0.05 g
Methotrexatum	Orally, intramuscularly or intravenously 0.03 g 2 times in a week, or 0.05 g once in five days	Coated tablets 0.002 5 g; ampoules 0.005, 0.05 or 0.1 g of powder for solution
Phthoruracilum	Intravenously slowly or drop-by-drop 0.01–0.015 g/kg once a day or once every 2 days	Ampoules 5 ml of 5 % solution
Vinblastinum (Rosevinum)	Intravenously 0.000 15–0.000 3 g/kg once per week	Ampoules 0.005 or 0.01 g of powder for solution
Vincristinum	Intravenously 0.000 01–0.000 03 g/kg once per week	Ampoules 1 or 5 ml of 0.1 % solution; vials 0.0005 or 0.001 g of powder for solution

RADIOPROTECTORS
RADIONUCLIDE DECORPORATION DRUGS

Radioprotectors are drugs which are used in case of radiation threat, during radiotherapy of cancer patients, and in work with radionuclides. Radioprotectors reduce or prevent the destructive action of ionizing radiation.

Radioprotectors are classified as follows.

1. Sulfur-containing drugs.

1.1. Sulfur-containing amino acids and their derivatives: *cysteine, methionine, cysteamine hydrochloride, taurine, acetylcysteine.*

1.2. Other groups of sulfur-containing drugs: *unithiol, β-mercaptoethylamide, isothiuronyl, cystophos, gamaphos, β-aminoethyl.*

2. Biogenic amines: *serotonin adipate, mexamine, adrenaline.*

3. Amino acids and their derivatives: *glutamic acid, asparaginic acid, Asparcamum, Panangin.*

4. Derivatives of nucleotides and nucleosides: *sodium nucleinate, methyluracil, phosphadenum, ATP, riboxinum.*

5. Alcohols: *butyl alcohol.*

6. Vitamins: *rutin, ascorbic acid, pyridoxine, tocopherol, nicotinamide, methylmethionine sulfonium.*

7. Antioxidants.

7.1. Antioxidants of direct action: *tocopherol, ubiquinone.*

7.2. Antioxidants of indirect action: *selenium-containing drugs, zinc-containing drugs, copper-containing drugs, amino acids, caffeine.*

8. Biopolymers: *zymosan.*

9. Estrogens: *estradiol.*

10. Polysacharides: *prodigiozan.*

11. Complexones: *pentacinum, tetacinum-calcium.*

12. Sorbents: *enterosorbent CKN, silica gel, activated carbon, carbolong, carbalose.*

13. Herbal preparations: *liquid extract and tincture of Ginseng, tinctures of Aralia, Chinese schizandra, Eleutherococcus, polyphenolic compounds.*
14. Methemoglobin-forming drugs: *sodium nitrite, methylene blue.*

According to duration of action, there are short-acting and long-acting radioprotectors. Short-acting radioprotectors develop effect in 0.5–4 hours after administration. These drugs protect from single radiation or short-term high-level radiation. Short-acting radioprotectors are administered in maximal doses. This group includes sulfur-containing compounds, biogenic amines, and methemoglobin-forming drugs which disrupt tissue oxygenation.

Long-acting radioprotectors are used to protect human body from long-term effects of low-level radiation. These drugs are divided into drugs with hypoxic mechanism of action and drugs with non-hypoxic mechanism of action. Drugs with hypoxic mechanism of action are biogenic amines and methemoglobin-forming drugs. Drugs with non-hypoxic mechanism of action include sulfur-contaning compounds and drugs of other groups.

Mexamine and *cysteamine hydrochloride* are drugs which are most commonly used to prevent and treat radiation sickness.

The damaging effect of ionizing radiation is lower in hypoxia. The drugs causing vasoconstriction and reducing oxygen blood concentration cause hypoxia and inhibit lipid peroxidation. These properties are typical for biogenic amines. These drugs are used to treat and prevent radiation sickness.

Mexamine is a biogenic amine which has a similar chemical structure to serotonin. Mexamine causes contraction of smooth muscles and provides sedating effect on the central nervous system. The drug is taken orally 30–40 minutes prior to radiation therapy. Mexamine is well tolerated by patients.

Sulfur-containing drugs contain SH_2-groups and are the most active radioprotectors. Sulfur-containing drugs inhibit free radicals in cell bodies, form compounds of heavy metals, normalize protein metabolism on the DNA level, and increase cAMP concentration.

Cysteamine hydrochloride is taken orally 1 hour prior to radiation therapy. The duration of the effect is 5 hours. The drug is used to prevent and treat chronic radiation sickness. Cysteamine hydrochloride is ineffective in cases of acute radiation sickness.

Cyanides also exhibit radioprotective effect due to blockage of respiratory enzyme cytochrome oxidase which provides transport of the electrons from cytochrome to oxygen.

Estrogens increase human body resistance to ionizing radiation. These drugs protect the bone marrow, thyroid gland, decrease catabolic action of ionizing radiation, and activate the immunity (phagocytosis).

Some macromolecular substances also have radioprotective activity (polysaccharides, nucleic acids, alcohols, and synthetic polymers). Their radioprotective effect arises 0.5–2 hours after intake and lasts up to 3 days. Mechanism of their action is based on stimulation of nucleic acid synthesis and bone marrow cell regeneration. Among glycans, *zymosan* is characterised by the highest radioprotective activity. Zymosan protects hematopoiesis from negative influence of antitumoral drugs and ionizing radiation. The drug is administered intramuscularly in dose 1–2 ml on alternate days. The treatment course is 5–10 injections.

Batilol protects leukocyte and erythrocyte sprouts from ionixing radiation within 4–6 weeks. The drug is taken orally together with butter or vegetable oil which improve batilol absorption.

Thesanum is used in skin protection from ionizing radiation. Liniment of thesanum is applied on the skin prior to radiation session.

Direct antioxidants are drugs with radiprotective properties: *tocopherol, ascorbic acid, nicotinamide, riboflavin, pyridoxine,* preparations of *Ginseng, Chinese magnolia, Manchurian Aralia, Eleutherococcus*, etc.

Selenium preparations are drugs with indirect antioxidant activity. Selenium stimulates enzymes of the antioxidant cellular

system (activates glutathione peroxidase and promotes synthesis of cytochrome C and ubiquinone).

Besides, antioxidant properties are typical for compounds of zinc and copper, glutathione precursors, linoleic acid, and caffeine.

Stimulators of leukopoiesis (*sodium nucleinate* and *methyluracil*) also provide radioprotective effect. Some radioprotective activity is typical for vasopressin, prostaglandins, and acetylcholine.

Chelators (*pentacinum, tetacinum-calcium,* and *alginates*), sorbents (*activated carbon, enterosorbent SKN, carbolong, silica gel*, etc.), pectins, vegetable fibers, and carboxymethyl cellulose bind radionuclides and provide their elimination from the body.

Step 1. Correct Answers to Tasks for Self-Control

Drugs Influencing Respiratory System

1. C.
2. A.
3. D.
4. E.
5. B.
6. E.
7. B.
8. E.
9. B.
10. C.
11. D.
12. E.
13. A.
14. D.
15. B.
16. A.

Cardiotonic Drugs

1. C.
2. A.
3. E.
4. C.
5. E.
6. E.
7. B.
8. A.
9. D.
10. E.
11. B.
12. E.
13. A.
14. C.
15. E.
16. A.
17. C.
18. B.

Antihypertensive and Hypertensive Drugs

1. B.
2. D.
3. E.
4. A.
5. A.
6. B.
7. E.
8. D.
9. B.
10. A.
11. C.
12. E.
13. A.
14. E.
15. B.
16. C.
17. E.
18. B.
19. C.
20. E.
21. A.
22. E.

Drugs to Treat Ischaemic Heart Disease (Antianginal Drugs)

1. E.
2. B.
3. E.
4. D.
5. C.
6. C.
7. E.
8. B.
9. D.
10. A.
11. C.
12. E.
13. D.
14. B.
15. C.
16. E.
17. A.
18. A.
19. C.
20. D.
21. C.
22. B.
23. D.
24. E.
25. D.
26. B.

Antiarrhythmic Drugs

1. B.
2. D.
3. E.
4. A.
5. B.
6. C.
7. E.
8. B.
9. B.
10. C.
11. B.
12. D.
13. A.
14. E.
15. C.
16. D.
17. A.
18. D.
19. C.
20. E.
21. B.

Drugs Influencing Digestive System

1. B.
2. C.
3. A.
4. E.
5. E.
6. B.
7. D.
8. E.
9. A.
10. C.
11. A.
12. D.
13. E.
14. B.
15. A.
16. B.
17. E.
18. C.
19. B.
20. D.
21. E.
22. E.
23. C.
24. E.
25. A.
26. D.
27. A.
28. E.
29. A.
30. E.
31. B.
32.E.
33. C.

Diuretic Drugs. Drugs Influencing Myometrium

1. B.
2. A.
3. E.
4. A.
5. D.
6. B.
7. E.
8. C.
9. D.
10. E.
11. C.
12. C.
13. A.
14. B.
15. D.
16. A.
17. D.
18. E.
19. C.
20. D.
21. D.

Drugs Influencing Erythro- and Leucopoesis

1. C.
2. A.
3. D.
4. E.
5. B.
6. E.
7. B.
8. D.
9. D.
10. B.
11. A.
12. A.

Drugs Influencing Blood Coagulation

1. B.
2. A.
3. E.
4. B.
5. D.
6. E.
7. A.
8. E.

Vitamins

1. E.
2. B.
3. A.
4. D.
5. C.
6. E.
7. A.
8. C.
9. E.
10. C.
11. E.

Hormonal Drugs

1. D.
2. A.
3. E.
4. C.
5. E.
6. C.
7. B.
8. D.
9. C.
10. A.
11. D.
12. E.
13. A.
14. D.
15. E.
16. C.
17. C.
18. A.
19. C.
20. E.
21. A.
22. E.
23. E.
24. E.
25. D.
26. C.
27. B.
28. D.
29. E.
30. B.
31. E.
32. C.
33. E.
34. D.
35. C.
36. E.
37. E.
38. B.
39. A.
40. D.
41. C.
42. E.
43. E.
44. C.
45. E.
46. A.
47. D.
48. B.
49. A.
50. E.
51. D.
52. B.
53. B.
54. B.
55. C.
56. B.
57.D.
58. E.
59. A.
60. D.
61. C.
62. E.
63. B.
64. C.
65. D.
66. E.
67. B.
68. C.
69. B.

Antiallergic and Immunotropic Drugs

1. B.
2. E.
3. C.
4. D.
5. D.
6. B.
7. C.
8. E.
9. A.
10. E.
11. C.
12. E.
13. A.
14. D.
15. C.
16. C.
17. E.
18. A.
19. B.
20. D.
21. E.
22. C.
23. B.
24. E.
25. B.
26. E.
27. B.
28. E.
29. C.
30. A.

Drugs to Treat Goat

1. B.
2. E.
3. C.
4. D.
5. E.
6. B.

Antiseptics and Disinfectants

1. D.
2. A.
3. B.
4. D.
5. E.
6. A.
7. C.
8. A.

Antibiotics

1. C.
2. A.
3. D.
4. E.
5. C.
6. E.
7. B.
8. D.
9. C.
10. E.
11. D.
12. D.
13. E.

Sulfonamides. Synthetic Antimicrobial Drugs

1. B.
2. A.
3. E.
4. D.
5. E.
6. B.
7. E.
8. D.
9. B.
10. C.

Antisyphilitic Drugs. Antituberculosis Drugs

1. A.
2. B.
3. A.
4. D.
5. D.
6. A.
7. D.

Antiviral, Antiprotosoal, and Antifungal Drugs

1. A.
2. D.
3. B.
4. E.
5. C.
6. B.
7. E.
8. B.
9. C.
10. D.
11. A.
12. B.
13. C.

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