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# The significance of selecting phytopreparations for individualized therapy of acute rhinosinusitis

The article is devoted to modern approaches to the treatment of acute rhinosinusitis taking into account the basic principles of the rational pharmacotherapy. Today acute rhinosinusitis (ARS) remains in the leading position among other diseases in outpatient practice, therefore, the choice of the optimal treatment tactics and the optimal drug in each clinical case is of particular importance. The drugs of choice for acute uncomplicated rhinosinusitis are herbal preparations. The phytopreparations have an effect on all links of the pathogenesis of the disease due to the complex action of their biologically active substances. The phytopreparation Sinupret® (Bionorica CE, Germany) is very often recommended by doctors and pharmacists for treating rhinitis, sinusitis and their complications. Priority of the choice of the drug is determined by its high efficiency and safety proven by numerous preclinical and clinical studies, the long experience of use and the presence of several dosage forms. Despite the common name each of the drugs of this brand has its own characteristics. They differ in the specificity of the dosage form, the physicochemical state of the active pharmaceutical substance, the dose of the active substances. Various Sinupret® modifications are important for the individualized rational pharmacotherapy of patients with ARS provided by both a physician and a pharmacist. When providing pharmaceutical care a pharmacist select over-the-counter medicines taking into account their effectiveness, safety, quality and economic expediency.

***Key words:*** acute rhinosinusitis; Sinupret®; rational pharmacotherapy; pharmaceutical care

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**Значення вибору фітопрепаратів для індивідуалізованої терапії гострих риносинуситів**

Висвітлені сучасні підходи до лікування гострих риносинуситів, які ґрунтуються на основних принципах раціональної фармакотерапії. Зважаючи на значну поширеність гострих риносинуситів, асоційованих з ГРВІ, особливого значення набуває вибір оптимальної тактики лікування та оптимального лікарського препарату у кожній клінічній ситуації. Препаратами вибору при гострих неускладнених риносинуситах вважаються рослинні препарати, які за рахунок комплексної дії біологічно активних речовин впливають на усі ланки патогенезу захворювання. Найбільш рекомендованим лікарями та фармацевтами фітопрепаратом є Синупрет® виробництва компанії Біонорика СЕ (Німеччина). Пріоритетність вибору препарату визначається його високою ефективністю та безпекою, які підтверджуються результатами численних доклінічних і клінічних досліджень, тривалим досвідом застосування, наявністю декількох лікарських форм. Незважаючи на загальну назву, кожен з препаратів цього бренду має свої особливості, які визначаються специфікою лікарської форми, фізико-хімічним станом активної фармацевтичної субстанції, дозою діючих речовин. Різноманіття модифікацій Синупрету® є важливим інструментом забезпечення індивідуалізованої раціональної фармакотерапії хворих на риносинусит не лише лікарем, але й фармацевтичним працівником, який у межах фармацевтичної опіки здійснює вибір безрецептурних лікарських препаратів з урахуванням їхньої ефективності, безпеки, якості та економічної доцільності.

***Ключові слова:*** гострий риносинусит; Синупрет®; раціональна фармакотерапія; фармацевтична опіка

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**Значение выбора фитопрепаратов для индивидуализированной терапии острых риносинуситов**

Освещены современные подходы к лечению острых риносинуситов, базирующихся на основных принципах рациональной фармакотерапии. Учитывая высокую распространенность острых риносинуситов, ассоциированных с ОРВИ, особое значение имеет выбор оптимальной тактики лечения и оптимального лекарственного препарата в каждом клиническом случае. Препаратами выбора при острых неосложненных риносинуситах считаются растительные препараты, которые благодаря комплексному действию биологически активных веществ влияют на все звенья патогенеза заболевания. Наиболее часто рекомендованным врачами и фармацевтами фитопрепаратом является Синупрет® производства компании Бионорика СЕ (Германия). Приоритетность выбора препарата определяется его высокой эффективностью и безопасностью, доказанными в многочисленных доклинических и клинических исследованиях, продолжительным опытом применения, наличием нескольких лекарственных форм. Несмотря на общее название, каждый из препаратов этого бренда имеет свои особенности, которые обусловлены спецификой лекарственной формы, физико-химическим состоянием активной фармацевтической субстанции, дозой действующих веществ. Разнообразие модификаций Синупрета® является важным инструментом обеспечения индивидуализированной рациональной фармакотерапии больных с риносинуситами не только врачом, но и фармацевтическим работником, осуществляющим в рамках фармацевтической опеки выбор безрецептурных лекарственных препаратов с учетом их эффективности, безопасности, качества и экономической целесообразности.

***Ключевые слова:*** острый риносинусит; Синупрет®; рациональная фармакотерапия; фармацевтическая опека

According to epidemiological studies and the competent opinion of many leading clinicians and scientists around the world, currently acute rhinosinusitis (ARS) remains in the leading position among other diseases in outpatient practice. It not only significantly reduces the patients' quality of life, but also has a significant socioeconomic impact [1, 2].

As a rule, ARS can be divided into common cold caused by viral infection (rhinoviruses, respiratory syncytial viruses, adenoviruses, coronaviruses, etc.) and post-viral rhinosinusitis. A small subgroup (only 0.5-2 % of patients) of the post-viral rhinosinusitis is caused by bacterial infection and is called acute bacterial rhinosinusitis (ABRS) [2, 3].

Irrespective of etiological (triggering) factors in the ARS pathogenesis the leading position belongs to the mucociliary clearance disorder. Its normal functioning allows evacuating the pathogenic microflora, foreign bodies, allergens, etc., with mucus from the nasal cavity and paranasal sinuses (PNS). The mucociliary clearance condition depends on the ciliated epithelium functional activity, which can be suppressed against the background of various exogenous and endogenous factors, including infections.

Thus, the virus penetration and replication in the cells of the nasal mucosa causes their death with release of inflammatory mediators that trigger the autoimmune cascade with involving of proinflammatory cytokines (interleukins-1 and interleukins-6, tumor necrosis factor, etc.). This leads to the loss of the ciliated epithelium function. The mucous membrane edema contributes to obstruction of the sinus ostia in the nasal cavity and result in the impaired sinus aeration and drainage. Against the background of inflammation, secretion stasis and partial pressure decrease in PNS the contact of the pathogen with the mucosa is prolonged. As a result, there are the optimal conditions for development of bacterial infection, further damage to the mucosal epithelium, manifestations of inflammation [1].

Changes in the rheological properties of the mucus produced by glass shaped mucous secreting cells are an equally important factor for development of ARS. In inflammation the qualitative composition of the mucus changes (the concentration of neutral and acidic glycoproteins increases, the water content decreases), which leads to an increased iviscosity and deteriorated fluidity of the mucus. At the same time, the mucus hyperproduction takes place. All this causes an inadequate mucociliary clearance and promotes accumulation of the pathological secret. A prolonged overload of the ciliated epithelium causes its dystrophy and atrophy. The vicious circle of ARS pathogenesis is closed [4, 5].

Taking into account the abovementioned facts the rhinogenous theory of RS pathogenesis is becoming increasingly popular in modern otolaryngology. On the basis of this theory, the treatment approaches of this disease are rethought. One of the main pathogenetic directions of RS therapy is the use of drugs with the secretomotoric and secretolithic activity, which provide the recovery of the "first line of defense" in PNS [6].

Sinupret® (Bionorica CE, Germany) represented at the pharmaceutical markets of more than 50 countries of the world is one of the well-known mucoactive drugs. It is a recognized leader in the frequency of prescriptions not only in Germany, but also in Ukraine for the treatment of rhinitis, sinusitis and their complications. According to the data of the company "Proxima Research" (Ukraine) specializing in the field of systematization of information and information provision of the pharmaceutical market in 2016 the number of Sinupret® recommendations by ENT-doctors was increased one and a half times, the number of Sinupret® recommendations by pediatricians was increased two and a half times compared to 2014. Sinupret® as an over-the-counter drug has its fans in pharmacy chains. The number of recommendations of this drug by pharmacists was increased twice for the period from 2012 to 2016 [7].

The secret of Sinupret® success is, first of all, in its recognizability, which is due to its evidence based effectiveness and safety. A convincing evidence base on the Sinupret® effectiveness and safety had its beginnings since 1933, i.e. from the beginning of its use in Germany. At the moment, Sinupret® is one of the most studied herbal drugs both in the pharmacological experiment and clinical trials [4, 5, 8, 9].

Until recently, at the pharmaceutical market of Ukraine Sinupret® was introduced only in tablets (Sinupret® and Sinupret®), syrup and drops for oral administration. Since 2017 the "Sinupret family" has been supplemented with one more drug in tablets by the trade name "Sinupret Extract®". Despite the common name each of the drugs of this brand has its own characteristics, which are determined by the dosage form, the state of the active pharmaceutical substance, the dose of the active substances.

All Sinupret® drugs are related to the original plant raw material, the qualitative composition of the active substances that determine their pharmacological activity. Sinupret® contains standardized extracts of five medicinal plants. They are Black elder (*Sambucus nigra*), Cowslip (*Primula versis/elatior*), Common sorrel (*Rumex species*), Vervain (*Verbena officinalis*) and Yellow gentian (*Gentiana lutea*). The high efficiency of each of the plants has been confirmed by the practical experience, and the therapeutic combination has subsequently been received a weighty scientific justification. Thanks to the unique combination of biologically active substances (BAS) of five medicinal plants Sinupret® has a versatile complex action, breaking the "vicious circle" in RS. The pharmacodynamics of Sinupret®

includes such major effects as secretomotoric, secretolithic, anti-inflammatory, antiinfective and immunomodulating action [4, 5, 8-11].

The secretolithic effect is characteristic for all plants that are part of phytocompositions. The main contribution to the mucoactive action belongs to BAS of the monoterpene class such as secoiridoid and bitter glycosides of Gentian root, iridoglygosides of vervain herb, cowslip and vervain saponins [8-12]. Thanks to the secretolitic action the ability of mucociliary clearance, which performs the most important protective role in infectious inflammatory diseases of PNS, is restored. Information about the direct secretomotoric action of Sinupret® has been obtained. The drug has the ability to increase the frequency of ciliary flicker and, thereby, improve mucociliary transport. The results of recent studies have shown the pronounced stimulating effect of the phytopreparation on the molecular regulatory systems of transport (CFTR-dependent transport) of chlorine ions in the respiratory epithelium, due to it the dose-dependent secretotolytic and secretory effects are implemented [13]. It has been proven that the secretolytic activity of Sinupret is comparable with the secretolitic activity of synthetic mucolytic drugs such as N-acetylcysteine, bromhexine, ambroxol [12, 13].

The essential supplement to the secretolytic activity of Sinupret is its anti-inflammatory potential, which is explained by the high content of flavonoids in all plants, and is supplemented by the presence of tannins and of gentian and verbena monoterpenes, gentian alkaloids, emodin and organic acids of sorrel, elderberry phenolic glycosides. Due to the complex action of BAS the inflammatory process development is suppressed, congestion is decreased, ventilation and drainage of PNS is restored. It is believed that the anti-cyclooxygenase component is one of the leading links in the mechanism of the anti-inflammatory action of Sinupret. It determines its influence on the primary links of inflammation, i.e. the exudation phase. As a result, inhibition of prostaglandin $E_2$ formation helps to reduce the permeability of the capillary wall, the mucous membrane edema and also promotes productive evacuation of the secretion [14].

The Sinupret action is focused on the cause of RS (viruses, bacteria), and it is both direct and indirect. The antimicrobial (antibacterial and antiviral) action is characteristic for sorrel herb due to the presence of emodin and oxalic acid, as well as primula and verbena due to the presence of saponins. The essential oils of gentian, primrose and verbena intensify this effect. The studies *in vitro* have shown that Sinupret has the bacteriostatic effect in relation to most of the known pathogens of ABRS such as *S. aureus* (including methicillin-resistant strains), *S. pyogenes*, *S. pneumoniae,* and the less effect against *H. Influenzae*. The antiviral effect of Sinupret® has also been found. The mechanism of this effect is due to the flavonoid component of verbena with the viricide effect preventing the virus replication, in particular influenza A, parainfluenza, respiratory-syncytial virus. In addition, against the background of the mucociliary transport activity recovery, the contact time of pathogens with the mucosa decreases, it prevents the virus adhesion and promotes the elimination of pathogens. An important advantage of the Sinupret antimicrobial action compared to other antibiotics is the absence of impact on the intestine saprophyte microflora and a low risk of formation of the pathogenic microorganisms resistance to the drug. In case of co-administration, Sinupret® potentiates the action of other antibacterial drugs, providing a more stable result of the ABRS etiotropic therapy. Along with the antiinfective effect, the phytopreparation exhibits the immunomodulating activity, i.e. indirectly interferes with the development of superinfection and reinfection. The immune profile of the drug includes stimulation of nonspecific defense factors, in particular phagocytosis; an increase of α and γ interferon production; increased level of IgA, lysozyme, T-helpers, etc. [8, 11, 15]. Thus, the Sinupret complex pharmacodynamics encompasses all the pathogenetic links of the RS, and it determines the predicted therapeutic effectiveness, namely reduction of the symptom severity, minimization of the disease duration, prevention of complications and development of chronic disease.

Despite the common pharmacodynamics, as well as the analogous indications for use all Sinupret® drugs has certain features that not only distinguish them from each other, but also determine the appropriateness of their use depending on the clinical situation.

Sinupret® drugs in the coated tablet form containing dried plants in the form of powder are the most well-known (commonly prescribed by doctors and popular among consumers). Sinupret® one tablet contains 78 mg of the plant powder, while Sinupret forte® contains 156 mg due to the double increase in the content of each of the components. Due to this, the drug has a longer duration of action, and the possibility to use one tablet (instead of Sinupret® two tablets) significantly increases the patient's compliance for the treatment. It should be noted that children over 12 years and adults are consumers of Sinupret forte®, while Sinupret® covers a wider range of patients, including children over 6 years. The necessary condition that provides the predicted effectiveness of Sinupret tablets in the ARS treatment in the presence of acute respiratory viral infection is its timely use (at the first signs of a common cold such as nose irritation, sneezing, nasal congestion, etc.). In this case, the antiadhesive effect of BAS

is more pronounced; the elimination processes are stimulated; in general, it will prevent development of pathology. If the time is lost, the hope for a quick achievement of the result is not always justified, then the course of treatment is extended, and in some cases antibiotics are added to the treatment. The use of Sinupret® in chronic inflammatory diseases of PNS is certainly justified not only by the high adequacy of its pharmacodynamics to the nature of the changes, but also by its high safety profile, harmlessness in the long-term use [16].

Sinupret® extract coated tablets are fundamentally different from their predecessors by the physical and chemical state of the pharmaceutical substance. One tablet contains 160 mg of a dry extract (3-6 : 1) from roots of gentian, primrose flowers, sorrel herb, elderberry flowers, verbena herb (1 : 3 : 3 : 3 : 3) (51 % ethanol as an extractant), it is equivalent to 720 mg of dried plants [16]. Thus, the dose of active substances in Sinupret® extracts exceeds more than four times of the dose in Sinupet forte®! By the quantitative content of flavonoids, which are the main fraction of BAS, the Sinupret® extract exceeds Sinupret forte® by 3.3 times and Sinuprept® by 10 times. Since it is the presence of flavonoids causes most of the pharmacological effects of the phytocomposition, the "dose-effect" direct proportional correlation can be traced on the example of Sinupret® extract; it is manifested in the study of the secretolitic activity most obviously. According to the experimental studies *in vitro* the increase of the extract concentration in the reaction medium (from 100 mg/ml to 1000 mg/ml) was accompanied with a significant "jump" of the chlorine ion concentration in the respiratory epithelium by activating its transport through CFTR-dependent channels. This ensures the efficiency of the transmembrane water transport and improvement of the rheological properties of the PPN secretion [18].

All pharmacodynamic effects of the traditional composition of 5 plants are typical for Sinupret® extract, and their intensity has a clear dose-dependence. In addition to the secretolytic effect intensification, the BAS dose increased by four times contributes to the dose-dependent increase of the antiviral and antimicrobial activity against typical infectious pathogens of the respiratory tract inflammation. The extract inhibits virus replication by 38-89 % *in vitro*, which is commensurable to the activity of synthetic antiviral drugs such as amantadine and ribavirin [18]. The minimum bactericidal concentration for MRSA, *Str.pneumoniae*, *H. influenzae* is 1 : 1000, it provides a powerful antibacterial effect of the drug when using it for the first time. For example, the experimental studies of Sinupret® show a decrease of bacterial growth only after four-day intake [19]. The experimental studies has confirmed the pronounced anti-inflammatory activity of Sinupret® extract and its significant inhibitory effect on cytokine-dependent mechanisms for formation of the inflammatory response [20], which is also of paramount importance for disease control, its rapid regression and the patient's recovery.

To confirm Sinupret® extract clinical efficacy several clinical multicenter studies of various design with the patient large population were conducted, in particular ARhiSi-1, ARhiSi-2, in which the treatment efficacy of patients with ARS treated with Sinupret® extract 480 mg per day (3 x 160 mg) was compared to placebo for 15 days [21]. The assessment of the patients' state showed that reduction of the ARS symptom (treatment response) was already observed on day 3 of the drug use, and on day 7 a statistically significant improvement of the state (by the amount of indicators) was achieved compared to placebo. The disappearance of the characteristic symptomatology and complete recovery were reported in 93.2 % of the patients on day 14, while when using placebo these indicators were in 85 % of the patients. It should be noted that the treatment period was reduced when Sinupret® extract was used. Most of the patients recovered on day 10, it was on 3.8 days earlier than in the placebo group. All of this is in favor of the pharmacoeconomic advisability of this drug use. An equally important characteristic of Sinupret® extract is its safety since a significant dose increase is most often associated with the increased risk of side effects. In clinical studies the drug tolerability was assessed by patients (94 %) and doctors (96 %) as "good" and "very good" and did not differ from the placebo-controlled one. In addition, there were no cases of the increased risk of undesirable events for more than 5 years of the clinical application of Sinupret® extract [21]. All of the above is a valid reason for the expediency of selecting Sinupret® extract as the "first aid" drug in case of uncomplicated ARS treatment in adults and children over 12 years old.

The possibility of additional choice among the Sinupret® products is expanding due to the presence of liquid dosage forms such as syrup and drops for internal use at the Ukrainian market. As is known, liquid dosage forms have a better bioavailability than solid dosage forms (for example, tablets) due to the dissolved state of the active substances. Release of the active substance from tablets occurs only after dissolution of the tablet coating and hydrolytic cleavage of plant tissues containing these BAS [22].

The syrup is specifically targeted to the children audience, starting with the age of 2. This dosage form significantly facilitates dosing depending on the child's weight and growth. Thus, 100 g of the syrup contains 10 g of the alcohol-water extract from medicinal plants and excipients (ethyl alcohol 8 %, purified water, cherry flavor, liquid maltitol). The content of alcohol in the drug (calculated with reference to a

daily dose) does not exceed its content in ordinary fruit juices for infant food, i.e. it does not have any risk to consumers. Maltitol gives the syrup a sweet taste. Maltitol is a sugar substitute, a food supplement included in the list of food additives; it does not adversely affect the human health and is allowed for use in the food industry of many countries of the world. In addition, syrup has a pleasant cherry flavor, therefore, well accepted by children. Despite the fact that the syrup is produced specifically for children, it can be used for the adult treatment in the absence of another dosage form at the market. Due to the content of maltitol the drug effect on the sugar level is insignificant; therefore, it can be used by patients with diabetes mellitus [16].

Sinupret® drops contain the alcohol-water extract of medicinal plants, 19 % ethyl alcohol, purified water, and are intended exclusively for internal use. Consumer categories are children over 2 years of age, and adults. There are no age limits for use in the adult population; the basis of choice is the patient's preferences. Drops are a form of choice for people who have problems with swallowing. They are not indicated for patients who are treated (were treated) for chronic alcoholism, and for patients with liver disease, and when the dose is exceeded, there is the increased risk for the children health, patients with epilepsy, organic brain diseases, etc. [16].

Proceeding from the principle of rationality in the tactics of pharmacotherapy of any disease, first of all, it is necessary to focus on a specific clinical situation (a particular patient). Only taking into account individual characteristics a reasonable choice of adequate medical products, dosage forms, doses and routes of drug administration, as well as the permissible duration of treatment is possible.

Various Sinupret® modifications are important for the individualized rational pharmacotherapy of patients with ARS provided by both a physician and a pharmacist. When providing pharmaceutical care a pharmacist select over-the-counter medicines taking into account their effectiveness, safety, quality and economic expediency.

As noted above, the drug of choice for the treatment of uncomplicated ARS (mainly common cold) is Sinupret® extract, which due to the "shock" dose of BAS has a powerful effect on the early stages of the disease and is highly effective even in monotherapy. The treatment efficacy of the extract was determined by reduction or complete absence of the ARS symptoms on day 5. The permissible period of the drug use in outpatient conditions is 7-14 days; if necessary, it can be prolonged by Sinupret® or Sinupret® forte. If the symptoms of ARS increase in 5 days of the disease or persist for more than 10 days, then it is a case of acute postvirus rhinosinusitis. The Sinupret® extract or the Sinupret® forte remain relevant for continuation of the treatment. Acute bacterial rhinosinusitis develops in about 2 % of these patients. It can be suspected by the state deterioration after minor ailment, the presence of purulent discharge from the nose, pronounced facial pain (headache). In this case, it is necessary to apply to the doctor and an adequate antibiotic therapy in combination with phytotherapy can be prescribed. In the acute period of relapsing ARS (from 1 to 4 episodes of ARS per year, the intervals between exacerbations are not less than 8 weeks without any symptoms at this time [23]) the use of Sinupret® forte is reasonable due to the prolonged action and the ease of use. In chronic rhinosinusitis (symptoms over 12 weeks) the expediency of the use of Sinupret® (or Sinupret® forte), which not only restores the PNS functional lability, but also increases the body's resistance to infections due to the immunomodulatory activity, has been clinically proven. The latter is important for the treatment of children who are often ill with acute respiratory infections, persons with impaired immunity [16].

When prescribing Sinupret® drugs it is appropriate to observe the principle of "targeting" depending on the age and the general condition of a patient. The young age patients with ARS who are active, have an active lifestyle and financially are not limited are the preferred target group of Sinupret® Extract consumers. Adults, regardless of age, who are commonly ill, are the group of Sinupret® and Sinupret® forte consumers. The efficacy and safety of these drugs do not decrease with the long-term use; therefore, they can be prescribed in each subsequent episode of the disease. Children as a special patient category are prescribed Sinupret® syrup and Sinupret® drops as children dosage forms. In addition, Sinupret® coated tablets can be given to children over 6 years [16].

The choice of the optimal medicinal product is only one of the components of the qualitative pharmacotherapy of ORS, which is supplemented by providing the patient with complete information about the effect of the selected drug, the way it is used (how, when, what doses, how long), possible side effects, compatibility with other medicines and food. There are no "good" or "bad" drugs since even the most effective drug may be inefficient due to incorrect selection and inadequate information about its use.

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