RESULTS OF MONITORING OF PRESCRIPTION OF POTENTIALLY DANGEROUS COMBINATIONS OF DRUGS IN PHARMACOTHERAPY UNDER INPATIENT TREATMENT

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Abstract: In case of combined pharmacotherapy, between drugs can occur interactions, which can be dangerous to the life and health of patients. Such combinations of drugs are considered to be one of the serious clinical problems, and are considered as errors that can be prevented. Therefore, it is relevant to determine the frequency of such appointments for further work on their prevention.

Aim of the research. Determine the structure and prevalence of the appointments of potentially dangerous combinations of drugs in the treatment of patients under inpatient treatment for further optimization of pharmacotherapy.

Materials and methods. In the automated mode, the lists of medical appointments of patients who were under inpatient treatment of 30 health facilities of Zhytomyr region in 2017 were monitored for the purpose of the simultaneous use of drugs, the interaction of which is dangerous. For further analysis by the levels of clinical significance using the Drug Interaction Checker system, the "Major" (hazardous) and "Moderate" (significant) combinations were selected on the Internet resource www.drugs.com. The frequency of the appointments of dangerous combinations, their prevalence by the nosological classes and the profiles of the offices of medical institutions was determined.

Results. As a result of the monitoring of 69405 cases, it was found that the average number of prescriptions per patient was 5.6±1.2 titles. In 1390 cases of treatment (2.0 % of 69405) simultaneously prescribed medicines, the interaction of which could be dangerous. In the structure of dangerous combinations, 81.5 % is taken with the simultaneous administration of drugs containing active substances ketorolac and pentoxifylline. The frequency of potentially dangerous appointments was greatest in the treatment of patients with diseases of the blood and blood-forming organs (D50-D89) – 11.6 %, in diseases of the musculoskeletal system and connective tissue (M00-M99) – 7.7 %, in diseases of the nervous system – 5.0 % of all cases of treatment.

Keywords: drugs, combined pharmacotherapy, potentially dangerous combinations, dangerous interactions, hospital, monitoring.

1. Introduction

When providing medical care doctors often use a combination of drugs. Prerequisites for this may be the presence of several illnesses in the patient (which is more typical for older people), as well as the inadequate efficacy or safety of monotherapy. At the same time, according to research results, combined administration of drugs sharply increases the risk of side effects [1, 2]. Introduction of 2 drugs leads to adverse drug reactions (ADR) due to interactions between drugs in 6 % of patients, and the use of 5 drugs increases their frequency to 50 %. When taking 10 medicines, the risk of drug interactions reaches 100 % [3]. In patients who took more than 6 drugs, intergroup interactions caused 59.1 % of all detected ADR [4].

Due to a significant increase in the use of medicines and their combinations, the corresponding increase in the frequency of drug interactions was noted. The interaction of drugs implies a change in the effectiveness and safety of one of them while simultaneously or sequentially with another drug [5, 6]. The interaction of drugs, which leads to increased efficiency and safety of pharmacotherapy, underlies the rational combination of drugs. However, the interaction can lead to a decrease in the effectiveness of pharmacotherapy, while talking about irrational combinations of drugs. And the bases of potentially dangerous combinations (PDC) are interactions that reduce the safety of pharmacotherapy. PDC drugs are considered one of the serious clinical problems [7, 8]. They are considered as errors that can be prevented, because in the instructions on the use of drugs this is indicated. There are open online resources, in some countries/hospitals, there is an appropriate software that warns physicians about the possibility of dangerous interactions between drugs that are prescribed to patients [9]. However, doctors do not always use the indicated capabilities; therefore, it is relevant to determine the frequency of cases of the administration of PDC drugs [10, 11]. This is necessary for further work on the prevention of such cases, as they are hazardous to the life and health of patients.

Aim of the research. To analyze the structure and prevalence of the appointments of potentially dangerous combinations of drugs in treating patients under inpatient treatment for further optimization of pharmacotherapy.

2. Methods

The study was conducted by continuous sampling and retrospective analysis in the automated medical records (lists of medical appointments) of 69405 patients who were under inpatient treatment of 30 healthcare facilities in Zhytomyr region in 2017 and received medication at the expense of the charity organization "Sickness fund of the Zhytomyr region" (SF) (prototype of the regional health insurance fund). From the lists of appointment of patients to the electronic database information was provided on the diagnosis with an indication of the cipher by ICD-10, designated trademarks of medicinal products, which were provided by the SF, the name of the department. The program contained an electronic directory of medicines in the form of drug groups and individual medicines for trade and international non-proprietary names (INNs), as well as a reference book of pairwise combinations of medicines by INNs, with the simultaneous appointment of which a dangerous interaction is possible. As a source of data on hazardous interactions was used "State Form of Medicines", issue 9 [12]. For automated monitoring of the presence of PDC drugs, reporting forms were developed using the Microsoft Access program.

In addition, in the first phase, cases of PDC were confirmed through the Drug Interaction Checker system of the online resource www.drugs.com [13], harmonized with the FDA's recommendations. Major combinations were selected for further analysis according to the levels of clinical significance (hazardous – potentially dangerous interactions between drugs: the risk of combined use of an ultrasound scanner exceeds the benefit for the

patient, therefore, in most cases it is necessary to avoid such combinations of drugs or to use drugs in minimal doses) and Moderate (significant interlaced interactions of medium importance: such combinations require more rigorous clinical, laboratory and instrumental control of efficiency and safety).

Only the drugs purchased by the SF were monitored (within the scope of the list, which included more than 800 trade names).

3. Results

As a result of the monitoring, 69405 electronic sheets of appointments of patients who received inpatient care in hospitals in Zhytomyr region during 2017 determined that 389 INN drugs were used in general, the average number of medical appointments was 5.6±1.2 preparations per one the patient. There were 1390 cases of drug PDC appointments (2.0 % of the total number of treated patients). After checking through the Drug Interaction Checker system, the online resource www.drugs.com refers to the 1282 combinations (92.2 %) to the Major group, and to the Moderate group 108 (7.8 %) (**Table 1**).

Table 1
Detected by monitoring results of the appointment of dangerous combinations of drugs

INN 1	INN 2	Number of appointments	Structure,%	Grading with Drug Interaction Checker
Ketorolac	Pentoxifylline	1133	81.5	Major
Ketorolac	Acetylsalicylic acid	70	5.0	Major
Ketorolac	Warfarin	5	0.4	Major
Theophylline	Pentoxifylline	60	4.3	Moderate
Gentamicin	Furosemide	38	2.7	Major
Gentamicin	Vancomycin	10	0.7	Moderate
Diphenhydramine	Metoprolol	36	2.6	Moderate
Warfarin	Clopidogrel	22	1.6	Major
Warfarin	Dipyridamole	2	0.1	Moderate
Verapamil	Sotalol	7	0.5	Major
Verapamil	Ivabradin	4	0.3	Major
Atorvastatin	Clarithromycin	2	0.1	Major
Ivabradin	Diltiazem	1	0.1	Major
Total		1390	100.0	

The frequency of potentially dangerous appointments was greatest in the treatment of patients with diseases of the blood and blood-forming organs (D50-D89) – 11.6 %, in the second place (the first – in absolute numbers) PDC was prescribed for diseases of the musculoskeletal system and connective tissue (M00-M99) – 7.7 %, in the third – diseases of the nervous system (5.0 % of all cases of treatment) (**Table 2**).

According to the frequency of PDC appointments, drug profiles were dominated by the neurological profile – 7.7 %, traumatological – 3.7 %, and surgical – 2.5 % (**Table 3**).

Table 2
Frequency of appointments of potentially dangerous combinations of drugs for nosological classes by ICD-10

Nosological classes by ICD-10	Number of treatment cases	Number of PDC appointments	Frequency, %
D50-D89: Diseases of the blood and blood-forming organs	190	22	11.6
M00-M99: Diseases of the musculoskeletal system and connective tissue	5689	439	7.7
G00-G99: Diseases of the nervous system	1921	96	5.0
S00-T98: Injury, poisoning and certain other consequences of external causes	3933	120	3.1
P00-P96: Certain conditions originating in the perinatal period	793	24	3.0
I00-I99: Diseases of the circulatory system	14239	398	2.8
E00-E90: Endocrine, nutritional and metabolic diseases	1204	30	2.5
L00-L99: Diseases of the skin and subcutaneous tissue	1339	22	1.6
K00-K93: Diseases of the digestive system	7606	92	1.2
A00-B99: Certain infectious and parasitic diseases	1118	13	1.2
C00-D48: Neoplasms	6630	57	0.9
Q00-Q99: Congenital malformations, deformations and chromosomal abnormalities	732	4	0.5
H60-H95: Diseases of the ear and mastoid process	404	2	0.5
O00-O99: Pregnancy, childbirth and the puerperium	5834	25	0.4
N00-N99: Diseases of the genitourinary system	5858	23	0.4
Other diseases	2571	8	0.3
H00-H59: Diseases of the eye and adnexaa	1219	2	0.2
J00-J99: Diseases of the respiratory system	8125	13	0.2
Total	69405	1390	2.0

Table 3
Frequency of appointments of potentially dangerous combinations of drugs on branch profiles

Department profile	Number of treatment cases	Number of PDC appointments	Frequency, %
neurological	6359	487	7.7
traumatological	2698	99	3.7
surgical	14170	349	2.5
resuscitation	6661	138	2.1
therapeutical	19242	224	1.2
maternity	2935	28	1.0
gynaecological	4641	34	0.7
urological	1359	6	0.4
otolaryngologic	1486	5	0.3
pediatric	5037	13	0.3
ophthalmic	1113	2	0.2
infectious	3003	5	0.2
Other	701	0	0.0
Total	69405	1390	2.0

4. Discussion

According to the results of the study, was noted a low frequency of appointments of drug combinations (only in 2.0 % of patients (1390 from 69405)), where the use of them may lead to dangerous interactions. The actual complications due to the appointments of these combinations have not been documented. The results we receive are much lower than the actual dangerous complications described by the authors with a frequency of 6.2 % [1] and 14.6 % [14]. The relatively low PDC in our study was due to a significant sample size (69405 cases), which included patients of different ages, and a small number of appointments per patient (5.6 drugs). This is significantly less than the result of 19.3 %, obtained by researchers through a retrospective analysis of 140349 hospitalizations [3]. In analyzing the PDC appointments in 200 patients over the age of 69 years [4], researchers report a result of over 75 % (patients received 7 drugs). The study [11] monitored the treatment of patients who prescribed more than 6 drugs, respectively, PDC were recorded in over 54 % of the hospitalized patients. In the study [5], the average number of appointments was more than 10, so prescribed PDC were over 71 % of patients. The reason for the small number of PDC detected in our study is the limited availability of input data (only drugs purchased for the funds of the "Sickness fund", for the treatment of the underlying disease and its complications) were taken into account, and the availability in medical institutions of doctors-experts in the "Sickness fund" carried out preliminary and current control over the rational use of drugs.

Among all the PDC found in our study, 81.5 % is a dangerous combination of drugs with active substances ketorolac and pentoxifylline, with the simultaneous administration of which significantly increases the risk of bleeding. This combination is most often prescribed for the provision of medical care in the departments of neurological, therapeutic, surgical profiles, in the treatment of patients with diseases of the musculoskeletal system and circulatory system. This indicates the need to inform doctors of different specialties about the dangers of the appointment of the combination, which will reduce the overall frequency of PDC appointments to 0.4 % of patients.

The conducted research confirmed the need for continuous monitoring of medical appointments regarding the presence of dangerous combinations and the introduction of a system for informing healthcare workers and the population about clinically significant drug interactions. This will increase the efficacy and safety of pharmacotherapy.

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