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Drug intolerance: age-related aspects

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ABSTRACT

BACKGROUND: Drug hypersensitivity is an adverse reaction caused by immune or non-immune mechanisms to the intake of adequate doses of drugs. To avoid a dangerous situation, correctly collected pharmacological history, taking into account all the characteristics of the patient (gender, age, concomitant pathology), and knowledge of the mechanism of action of drugs can help a practicing physician who does not currently have a reliable method for diagnosing drug hypersensitivity.

AIM: Identification of age-specific drug intolerance.

MATERIALS AND METHODS: The study was conducted from 2017 to 2020 and included 200 outpatient medical history forms of individuals diagnosed with an unspecified pathological reaction to a drug or medication. All drug reactions were based on patient's own statements and were allocated as dichotomous variables. The results were analyzed by non-parametric statistics (Pearson's chi-square).

RESULTS: Three groups of patients were identified: 18–44 years (n=49), 45–60 years (n=60), ⩾61 (n=91). The odds of incomprehensible reactions were 2.2 times higher in patients in group 3 than in patients in the other groups. Group 3 patients were 12 times more likely to have an itchy reaction to medications than patients in the other groups. Group 1 patients were 3 times more likely to have urticaria than patients in groups 2 and 3. The odds of drug intolerance to angiotensin-converting enzyme (ACE) inhibitors were 2.6 times higher in patients in group 3 than in patients in the other groups. When comparing clinical manifestations of drug intolerance to penicillin and cephalosporin antibiotics, no significant differences were found in all patients. The presence of allergies and somatic pathology of ⩾3 systems did not significantly affect the possibility of reactions of varying severity to ⩾3 drugs in these groups.

CONCLUSIONS: Patient's age has no effect on the possibility of reactions to certain groups of drugs. The exception was ACE inhibitors, which is most likely due to the higher frequency of prescribing antihypertensive therapy in patients in this age group. The aggravation of clinical manifestations and the occurrence of polypharmacy are not associated with age and comorbid background. Age and non-life-threatening clinical manifestations of drug intolerance were correlated, which indicates the absence of the reliable effect of age on the possibility of anaphylactic shock or angioedema.

Keywords: drug intolerance; drug allergy; drug hypersensitivity; age

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Возрастные аспекты реакций на лекарственные препараты

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АННОТАЦИЯ

ОБОСНОВАНИЕ. Лекарственная гиперчувствительность представляет собой обусловленные иммунными или неиммунными механизмами нежелательные реакции на приём адекватных доз лекарственных препаратов. Практикующему врачу, не имеющему на сегодняшний день достоверного метода диагностики лекарственной гиперчувствительности, поможет избежать опасной ситуации только правильно собранный фармакологический анамнез с учётом всех характеристик пациента (пол, возраст, сопутствующая патология) и знание механизма действия лекарственных средств.

ЦЕЛЬ — выявить возрастные особенности реакций на лекарственные препараты.
МАТЕРИАЛ И МЕТОДЫ. Исследование проводилось в период с 2017 по 2020 г. В исследование включены 200 амбулаторных карт пациентов с диагнозом «Патологическая реакция на лекарственное средство или медикаменты, неуточнённая». Данные фармако-аллергологического анамнеза указывались только на основании информации, полученной от пациента и, возможно, ранее выставленного в другом ЛПУ диагноза лекарственной гиперчувствительности. Все реакции на лекарственные препараты были распределены по дихотомическим переменным. Результаты исследований проанализированы методом непараметрической статистики (хи-квадрат Пирсона).
РЕЗУЛЬТАТЫ. Выделены 3 группы пациентов: 18–44 года (n=49); 45–60 лет (n=60); 61 год и старше (n=91). У пациентов 3-й группы вероятность появления зуда и не обусловленных гиперчувствительностью реакций на лекарственные препараты выше, чем у других, в 12 и 2,2 раза соответственно. Пациенты 1-й группы в 3 раза чаще подвержены развитию крапивницы, чем участники групп 2 и 3, а вероятность реакций на ингибиторы ангиотензинпревращающего фермента выше в 2,6 раза у пациентов 3-й группы. При сравнении клинических проявлений лекарственной гиперчувствительности на антибиотики пенициллинового и цефалоспоринового ряда достоверных различий между пациентами не выявлено. Наличие аллергии и соматической патологии трёх и более систем у пациентов наблюдаемых групп достоверно не повлияло на возможность возникновения реакций разной степени тяжести при приёме ⩾3 препаратов одновременно.
ЗАКЛЮЧЕНИЕ. Возраст пациента не оказывает влияния на вероятность возникновения реакций на определённые группы препаратов (исключением стали ингибиторы ангиотензинпревращающего фермента, что, скорей всего, обусловлено более высокой частотой назначения антигипертензивной терапии у пациентов данной возрастной группы). С возрастом и коморбидным фоном не связаны ни усугубление клинических проявлений, ни возникновение полипрагмазии. Выявленная корреляционная зависимость между возрастом и не угрожающими жизни клиническими проявлениями реакций на лекарственные препараты свидетельствует об отсутствии достоверного влияния возраста на возможность возникновения анафилактического шока или ангионевротического отёка.

Ключевые слова: реакции на лекарственные препараты; лекарственная аллергия; лекарственная гиперчувствительность; возраст

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Background

Drug-induced hypersensitivity remains an urgent problem in practical health care due to the risk of severe allergic reactions, which often require hospitalization or long-term treatment [1].

In clinical practice, adverse drug reactions occur in 0.04–3.1% of patients. One in 4,000 patients who visits the emergency department is admitted with a life-threatening condition after medication intake [2].

There are two types of adverse drug reactions, namely those related (type A, predictable reactions) and unrelated (type B, unpredictable reactions) with the pharmacological action of the drug [3–5]. Predictable reactions are more common and are related to dose, pharmacological effect, and cross-reactions between concurrently administered drugs. Unpredictable reactions are less common (20–25% of patients) and are due to the individual characteristics of the patient. This type of reaction includes non-allergic congenital hypersensitivity (idiosyncrasy) and drug-induced hypersensitivity (allergic and non-allergic).

Drug-induced hypersensitivity represents adverse reactions to the intake of adequate doses of drugs caused by immune (drug allergy) or non-immune (non-allergic drug hypersensitivity) mechanisms [6, 7]. Given the lack of a reliable method for diagnosing drug-induced hypersensitivity nowadays [8–10], it must be admitted that only a correctly collected pharmacological history, including all patient characteristics (gender, age, concomitant pathology) and awareness of the mechanism of drug action, will help the practicing physician to avoid a hazardous situation. [11].

Currently, the risk factors that contribute to the development and aggravation of the course of drug-induced hypersensitivity include genetic predisposition, demographic characteristics, and comorbid conditions. Among the demographic risk factors, which include female gender, race, and old age, only the latter, according to several authors, is the most unfavorable and is associ-

ated with the severity and prevalence of drug-induced hypersensitivity cases [12–15].

This work aimed to identify age-related characteristics of drug-induced reactions.

Materials and methods

Study design

An observational single-center cohort uncontrolled retrospective study was performed. The study design diagram is presented in Fig. 1.

Inclusion criteria

The criterion for inclusion of patients in the study was reactions to one or more drugs with a diagnosis of unspecified pathological reaction to a drug or drugs.

Conditions of conducting

In the Regional Clinical Hospital No. 1 (Tyumen) of the Tyumen region, 200 outpatient patient records were selected and analyzed.

Study duration

The study was performed for three years (2017 to 2020).

Description of the medical intervention

Out of 3650 primary outpatient records of patients, the outpatient records of 200 patients (171 women and 29 men) with a diagnosis T88.7 (unspecified pathological reaction to a drug or drugs) according to ICD-10 were included in the study and analyzed.

The anamnesis data of 200 patients were entered into a table with the columns indicating full name, age, gender, place of residence, the name of the drug which induced the reaction, clinical manifestations of drug-induced hypersensitivity, namely urticaria, angioneurotic edema, cough, choking, dermatitis, anaphylactic shock; other manifestations of drug-induced hypersensitivity such as dizziness, tinnitus, headache, tachycardia, deterioration in the condition, dyspeptic disorders; somatic pathology in the ENT organs, respiratory (chronic obstructive pulmonary

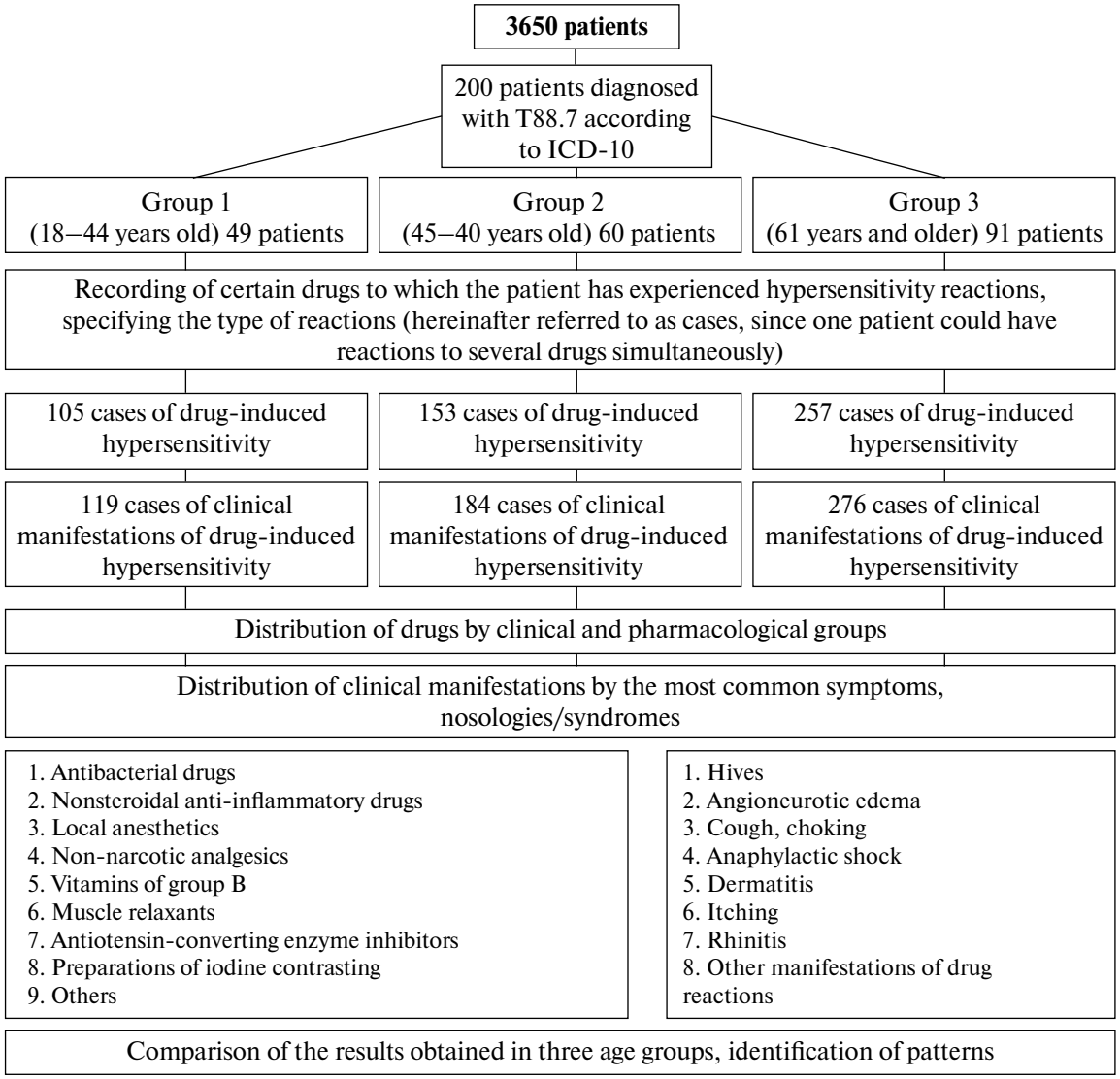

Fig. 1. Study design diagram.

disease), cardiovascular, digestive, genitourinary, nervous, and endocrine systems; helminthiases, hematological, oncological, autoimmune diseases; allergopathology including allergic rhinitis, urticaria, angioneurotic edema, bronchial asthma (sensitization and eosinophilia were indicated separately). In addition, all columns except full name, age, place of residence, the name of the drug which induced the reaction, eosinophilia, and helminthiasis were filled with dichotomous variables (presence of a disease/reaction — 1; no disease/reaction — 0).

Main study outcome

The aspects of drug-induced hypersensitivity were revealed in patients of different age groups, namely in young patients (18–44 years old), middle-aged patients (45–60 years old), elderly and senile patients (61 years and older).

Additional study outcomes

The most common groups of drugs causing adverse reactions and the range of these reactions were identified in patients of different age groups, namely in young patients (18–44 years old), middle-aged patients (45–60 years old), elderly and senile patients (61 years and older).

Subgroup analysis

Three age groups of patients were formed according to the criteria of the World Health Organization, namely 18–44 years implied young age (n = 49); 45–60 years indicated middle-aged patients (n = 60); 61 years and older corresponded to elderly and senile patients (n = 91). Age was indicated at the time of the patient's visit.

Outcome registration methods

All reactions to drugs and the presence of comorbidities were recorded according to the information provided by the patients and distributed according to dichotomous variables (the presence of a disease/reaction — 1; no disease/reaction — 0). Each episode of reaction to one drug that occurred within one year after the patient's visit was taken as a unit and considered a case (a total of 515 cases were identified). The distribution of drugs into groups was performed according to the clinical and pharmacological characteristics. The groups were formed provided that the drug was indicated three times or more (except for drugs for anesthesia ketamine and midazolam). All other drugs were assigned to the "Others" group. We have identified 33 groups of drugs.

The distribution of drugs by groups and subgroups is presented in Table 1.

Ethical considerations

Conclusion of the protocol of the Ethics Committee at the Tyumen State Medical University No. 100 dated 06/11/2021 indicated that "Based on the analysis of the documentation submitted, the Ethics Committee at the Tyumen State Medical University decided that, given the non-interventional nature of the study, this study does not require ethical examination."

Statistical analysis

Principles for calculating the sample size. The sample size was not pre-calculated.

Methods of statistical data analysis included Microsoft Excel (Microsoft, USA) and STATISTICA 6.0 (StatSoft Russia, Russia) software for data processing. We analyzed the results of the studies using the methods of nonparametric statistics. Descriptive statistics were performed by estimating the arithmetic mean (M) and mean-square deviation ($M \pm s$). To assess intergroup differences, given categorical data, calculations were made using four-field tables. The rows represented the factor values (age ranges) and the columns represented the outcome values. Depending on the smallest value of the expected event (out of four), the analysis method was chosen as follows. If the smallest value of the expected event was less than 5, Fisher's exact test was used for comparison; if the smallest value of the expected event was within the range from 5 to 10, Yates continuity-corrected Pearson's chi-square test was used for comparison; if the smallest value of the expected event was more than 10, the Pearson chi-square test was chosen. To quantify the dependence of the probability of an outcome on the presence of a factor, the odds ratio was calculated with a 95% confidence interval (CI). The critical significance level of the null statistical hypothesis p (the absence of differences and influences) was taken equal to 0.05.

Results

Objects (participants) of the study

The study analyzed 200 outpatient records of patients (171 women and 29 men) whose average age was 55 ± 15 years (range: 18–85 years).

Clinical and demographic characteristics of patients are presented in Table 2.

Key research outcomes

Clinical manifestations of adverse drug reactions

The distribution of clinical drug-induced manifestations in each age group did not differ significantly. However, reactions in the form of angioneurotic edema and dermatitis were among the three most common reactions in each group, namely 27.73% and 14.29% in group 1; 22.28% and 21.74% in group 2; and 19.57% and 21.38% in group 3, respectively.

In group 1, along with angioneurotic edema, there were reactions in the form of urticaria (27.73%), in the p 2, there were coughing and choking (15.76%), and in group 3, other manifestations of drug-induced reactions prevailed (22.83%); Table 3.

Comparison of clinical manifestations of drug-induced reactions in patients of three age groups demonstrated significant differences in the number of reactions (Fig. 2).

Other manifestations of adverse drug reactions (dizziness, tinnitus, headache, tachycardia, deterioration

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Table 1. Drugs for which hypersensitivity have been reported

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
1	Non-narcotic analgesics		Acetylsalicylic acid + paracetamol (Citramon)	4 (0.78)	18.18
			Metamizole sodium	13 (2.52)	59.09
			Paracetamol	5 (0.97)	22.73
2	Opioid analgesics		Tramadol	1 (0.19)	25.00
			Fentanyl	3 (0.58)	75.00
3	Angiotensin 2 receptor antagonists	AT2 inhibitors	Valsartan	1 (0.19)	33.33
		AT2 inhibitors	Losartan	2 (0.39)	66.67
4	Antimicrobial drugs	Aminoglycosides	Streptomycin	2 (0.39)	100.00
		Amphenicols	Chloramphenicol	5 (0.97)	100.00
		Ansamycins	Rifaximin	1 (0.19)	100.00
		Macrolides	Azithromycin	1 (0.19)	14.29
			Clarithromycin	3 (0.58)	42.86
			Erythromycin	3 (0.58)	42.86
		Unspecified	Unspecified	1 (0.19)	100.00
		Nitrofurans	Nifurantel	1 (0.19)	50.00
			Furazidin	1 (0.19)	50.00
		Penicillins	Amoxicillin	11 (2.13)	22.92
			Ampicillin	2 (0.39)	4.17
			Amoxiclav	1 (0.19)	2.08
			Unspecified	34 (6.59)	70.83
		Tetracyclines	Doxycycline	4 (0.78)	66.67
			Tetracycline	2 (0.39)	33.33
		Fluoroquinolones	Levofloxacin	2 (0.39)	2.02
			Ciprofloxacin	5 (0.97)	5.05
		Cephalosporins	Cefazolin	2 (0.39)	10.00
			Cefexime	2 (0.39)	10.00
			Cefotaxime	4 (0.78)	20.00
			Ceftazidime	1 (0.19)	5.00
			Ceftriaxone	6 (1.16)	30.00
			Unspecified	5 (0.97)	25.00

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Table 1. Continuation

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
5	Antibacterial sulphanilamide drugs		Co-trimoxazole	3 (0.58)	75.00
			Sulfanilamide	1 (0.19)	25.00
6	Antihypertensive drugs	Central vasodilators	Moxonidine	3 (0.58)	75.00
		Peripheral vasodilators	Reserpine	1 (0.19)	25.00
7	Antihistamines		Desloratadine	1 (0.19)	6.25
			Diphenhydramine	9 (1.74)	56.25
			Loratadine	1 (0.19)	6.25
			Fenspiride	1 (0.19)	6.25
			Chloropyramine	3 (0.58)	18.75
			Cetirizine	1 (0.19)	6.25
8	Antioxidants		Ab to S100 protein. Ab to endothelium NO-synthase	1 (0.19)	14.29
			Ethylmethylhydroxypyridine succinate	6 (1.16)	85.71
9	Antiseptics		Potassium permanganate	1 (0.19)	25.00
			Strepsils (amylmetacresol + dichlorobenzyl alcohol)	1 (0.19)	25.00
			Chlorhexidine bigluconate	1 (0.19)	25.00
			Ethanol	1 (0.19)	25.00
10	Ca-channel blockers		Lecarnidipine	2 (0.39)	33.33
			Nifedipine	4 (0.78)	66.67
11	Broncholytic drug. phosphodiesterase inhibitor		Aminophylline	8 (1.55)	100.00
12	β_1-adrenergic receptor blockers		Bisoprolol	2 (0.39)	66.67
			Metoprolol	1 (0.19)	33.33
13	Venotonic		Diosmin	1 (0.19)	33.33
			Troxerutin	1 (0.19)	33.33
			Thiamine + escin	1 (0.19)	33.33
14	B vitamins		Group B vitamins	41 (7.95)	100.00

Table 1. Continuation

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
15	GCS		Dexamethasone	2 (0.39)	28.57
			Prednisone	4 (0.78)	57.14
			Triamcinolone	1 (0.19)	14.29
16	ACE inhibitors		Captopril	3 (0.58)	14.29
			Lisinopril	3 (0.58)	14.29
			Perindopril	6 (1.16)	28.57
			Enalapril	8 (1.55)	38.10
			Unspecified	1 (0.19)	4.76
17	Macro and trace elements		Calcium gluconate	1 (0.19)	7.69
			Calcium chloride	5 (0.97)	38.46
			Calcium + Vitamin D	1 (0.19)	7.69
			Magnesium sulfate	4 (0.78)	30.77
			Multivitamins	1 (0.19)	7.69
			Ferrum Lek	1 (0.19)	7.69
18	Local anesthetics	Paraaminogroup	Lidocaine	30 (5.81)	49.18
		Amides	Novocaine	31 (6.01)	50.82
19	Metabolic drugs		Inosine	5 (0.97)	62.50
			Mildronate	3 (0.58)	37.50
20	Muscle relaxants		Baclofen	1 (0.19)	8.33
			Rocuronium	2 (0.39)	16.67
			Suxamethonium chloride	1 (0.19)	8.33
			Tizanidine	3 (0.58)	25.00
			Tolperisone	5 (0.97)	41.67
21	Myotropic antispasmodics		Dibasol	1 (0.19)	25.00
			Drotaverine	1 (0.19)	25.00
			Mebeverine	1 (0.19)	25.00
			Papaverine	1 (0.19)	25.00
22	Nootropic drugs		Aminophenyl-butyric acid	1 (0.19)	80.00
			Piracetam	4 (0.78)	20.00

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Table 1. Continuation

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
23	NSAID	Comb. NSAIDs	Dexketoprofen	1 (0.19)	50.00
			Paracetamol + Ibuprofen	1 (0.19)	50.00
		Topical NSAIDs	Benzidiamine hydrochloride	1 (0.19)	100.00
		NSAIDs (mainly COX-2 selective)	Meloxicam	7 (1.36)	46.67
			Nimesulide	7 (1.36)	46.67
			Etoricoxib	1 (0.19)	6.67
		NSAIDs (COX-1. 2 non-selective)	Aceclofenac	2 (0.39)	5.56
			Acetylsalicylic acid	13 (2.52)	36.11
			Diclofenac	10 (1.94)	27.78
			Ibuprofen	3 (0.58)	8.33
			Ketoprofen	3 (0.58)	8.33
			Ketorolac	3 (0.58)	8.34
			Lornoxicam	1 (0.19)	2.78
			Tenoxicam	1 (0.19)	2.78
		Unspecified	Unspecified	4 (0.78)	100.00
24	Plasma-substituting agents		Rheopolyglucin	3 (0.58)	100.00
25	Cartilage tissue regeneration stimulating drug		Glucosamine + chondroitin	1 (0.19)	33.33
			Chondroitin	2 (0.39)	66.67
26	Intravenous anesthesia agents		Propofol	3 (0.58)	100.00
27	Non-inhalation anesthesia agents		Ketamine	1 (0.19)	100.00
28	Iodine-contrast agents		Radiopaque diagnostic agent for intravascular and intracavitary administration	23 (4.45)	100.00
29	Anti-inflammatory drugs used to treat NUC and Crohn's disease		Sulphasalazine	3 (0.58)	100.00

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Table 1. Ending

№	Drug group	Subgroup	Drug name	Number of cases of drug intolerance to this drug. *n* (%)	Number of cases of drug intolerance to this drug within the subgroup/group. %
30	Microcirculation improving drugs		Betahistine	1 (0.19)	25.00
			Pentoxifylline	3 (0.58)	75.00
31	Antiviral drugs	HIV treatment drugs	Raltegravir	1 (0.19)	50.00
			Etravirine	1 (0.19)	50.00
		Antiviral/antihistamine drugs	Abs to human interferon-gamma. Abs to histamine. Abs to CD4	1 (0.19)	16.67
		Antiviral drugs	Dioxotetrahydrooxytetrahydro-naphthaline	1 (0.19)	16.67
		Antiviral drugs	Pentandioic acid imidazolyl ethanamide	1 (0.19)	16.67
		Antiviral drugs/interferon inducers	Meglumine acridone acetate	1 (0.19)	16.67
		Antiviral drugs	Rimantadine	1 (0.19)	16.67
		Antiviral drugs/interferon inducers	Tilorone	1 (0.19)	16.67
32	Dormitive and sedative drugs for premedication and anesthetic induction		Midazolam	1 (0.19)	100.00
33	Animal origin agents		Aprotinin	1 (0.19)	9.09
			Bioactive sea fish concentrate	1 (0.19)	9.09
			Deproteinized calf blood hemoderivative	4 (0.78)	36.36
			Lanolin cream	1 (0.19)	9.09
			Pig brain peptides	3 (0.58)	27.27
			Tetanus toxoid	1 (0.19)	9.09
34	Other			43 (8.33)	8.33

Note. Ab — antibodies; GCS — glucocorticoid steroids; ACE inhibitors — angiotensin-converting enzyme inhibitors; NSAIDs — nonsteroidal anti-inflammatory drugs; COX-2 — cyclooxygenase-2; NUC — nonspecific ulcerative colitis; HIV — human immunodeficiency virus.

Table 2. Clinical and demographic characteristics of patients

Indicator	All subjects	Group 1 18–44 years *n* = 49	Group 2 45–60 years *n* = 60	Group 3 61 years and older *n* = 91
Men. *n* (%)	29 (14.5)	11 (22.45)	8 (13.33)	10 (10.99)
Women. *n* (%)	171 (85.5)	38 (77.55)	52 (86.67)	81 (89.01)
Somatic pathology. *n* (%)	**183 (91.5)**	**40 (81.63)**	**56 (93.33)**	**87 (95.6)**
CVS pathology. *n* (%)	100 (54.64)	4 (10)	32 (53.33)	64 (70.33)
UGS pathology. *n* (%)	67 (36.61)	12 (30)	22 (36.67)	33 (36.26)
GIT pathology. *n* (%)	62 (33.88)	12 (30)	23 (38.33)	27 (29.67)
Endocrine pathology. *n* (%)	56 (30.60)	7 (17.5)	20 (33.33)	29 (31.87)
Pathology of the hepatobiliary system. *n* (%)	43 (23.50)	8 (20)	11 (18.33)	24 (26.37)
Respiratory system pathology (COPD. BOS). *n* (%)	31 (16.94)	3 (7.5)	8 (13.33)	20 (21.98)
NS pathology. *n* (%)	30 (16.39)	8 (20)	9 (15)	13 (14.29)
Helminthiasis. *n* (%)	30 (16.39)	10 (25)	7 (11.67)	12 (13.19)
ENT pathology. *n* (%)	20 (10.93)	9 (22.5)	6 (10)	7 (7.69)
US pathology. *n* (%)	17 (9.29)	4 (10)	5 (8.33)	8 (8.79)
Oncology. *n* (%)	11 (6.01)	1 (2.5)	2 (3.33)	8 (8.79)
Autoimmune diseases. *n* (%)	10 (5.46)	2 (5)	3 (5)	5 (5.49)
Blood pathology. *n* (%)	9 (4.92)	2 (5)	4 (6.67)	3 (3.3)
Allergic pathology. *n* (%)	**38 (19)**	**9 (18.37)**	**13 (21.67)**	**16 (17.58)**
Allergic rhinitis. *n* (%)	19 (50)	5 (55.56)	7 (53.85)	7 (43.75)
Dermatitis. *n* (%)	12 (31.58)	2 (22.22)	5 (38.46)	6 (37.5)
Urticaria. *n* (%)	6 (15.79)	1 (11.11)	1 (7.69)	4 (25)
Angioneurotic edema. *n* (%)	6 (15.79)	1 (11.11)	3 (23.08)	2 (12.5)
Bronchial asthma. *n* (%)	6 (15.79)	2 (22.22)	6 (46.15)	6 (37.5)

Note. CVS — cardiovascular system; UGS — urogenital system; GIT — gastrointestinal tract; COPD — chronic obstructive pulmonary disease; BOS — broncho-obstructive syndrome; NS — nervous system; US — urinary system.

Table 3. Clinical manifestations of drug hypersensitivity

Clinical manifestations of drug-induced hypersensitivity	All subjects	Group 1 18–44 years	Group 2 45–60 years	Group 3 61 years and older
Total number of cases of clinical manifestations, n.	579	119	184	276
Angioneurotic edema, *n* (%)	128 (22.11)	33 (27.73)	41 (22.28)	54 (19.57)
Dermatitis, *n* (%)	116 (20.03)	17 (14.29)	40 (21.74)	59 (21.38)
Other manifestations, *n* (%)	98 (16.93)	12 (10.08)	23 (12.50)	63 (22.83)**
Urticaria, *n* (%)	85 (14.68)	33 (27.73)*	25 (13.59)	27 (9.78)
Anaphylactic shock, *n* (%)	69 (11.92)	16 (13.45)	24 (13.04)	29 (10.51)
Cough and choking, *n* (%)	61 (10.54)	7 (5.88)	29 (15.76)	25 (9.06)
Itching, *n* (%)	12 (2.07)	0 (0)	1 (0.54)	11 (3.99)**
Rhinitis, *n* (%)	10 (1.73)	1 (0.84)	1 (0.54)	8 (2.90)

Note. * $p < 0.05$ if data of the 1st group were compared with two other groups; ** $p < 0.05$ if data of the 3rd group were compared with two other groups. The table does not include patients (17 people: groups 1 and 2 — for two people; group 3 — 13 people) with cough while taking an ACE inhibitor.

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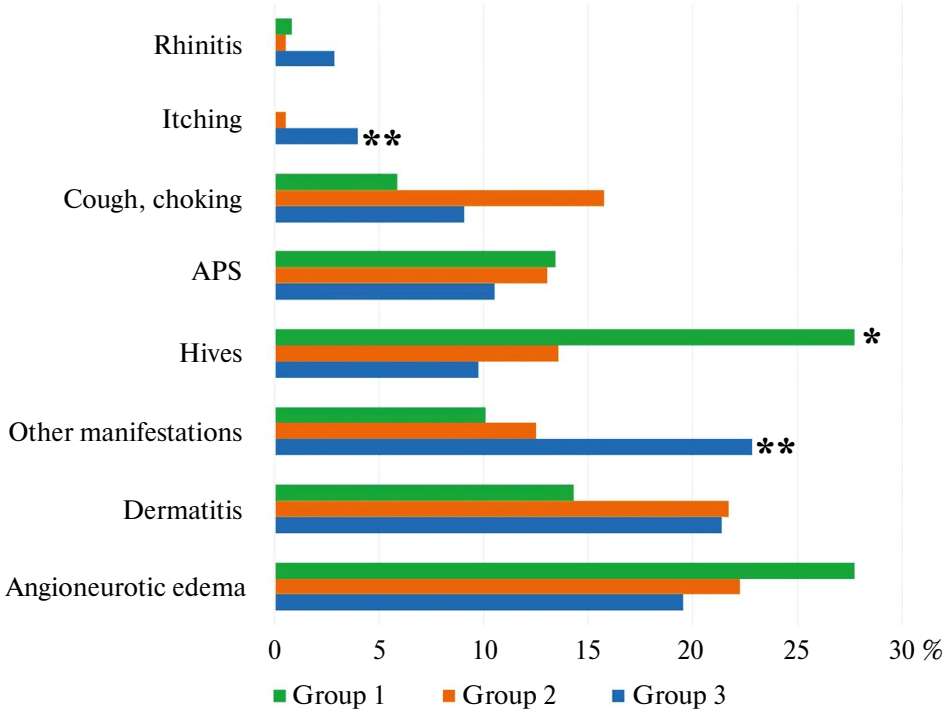

Fig. 2. Clinical manifestations of drug intolerance in all patients.

Note: * p <0.05 if data of the 1st group were compared with two other groups; ** p <0.05 if data of the 3rd group were compared with two other groups; АФШ — anaphylactic shock. This diagram did not include a cough response to ACE inhibitors.

of the condition, dyspeptic disorders) in elderly and senile patients were registered in 63 (22.83%) cases, while in other groups, these were in 35 cases (10.08% in the group 1 and 12.50% in the group 2). The differences in indicators assessed using Pearson's chi-square test were statistically significant (p = 0.001). The probability of other manifestations of drug-induced hypersensitivity in elderly and senile patients was 2.2 times more likely than in younger patients (95% CI 1.382–3.395).

Reactions in the form of drug-induced itching in elderly and senile patients were noted in 11 (3.99%) cases, while in patients of other ages, they were registered in one case (0.54% in group 2). The differences in indicators evaluated using Yates corrected Pearson's chi-square test was statistically significant (p = 0.007). Elderly and senile patients were 12 times more likely to develop drug-induced itching than younger patients (95% CI 1.553–94.391).

Drug-induced urticaria in young patients occurred in 33 (27.73%) cases and in 52 cases in patients of other ages (13.59% in group 2 and 9.78% in group 3). The differences in indicators assessed using Pearson's chi-square test were statistically significant (p < 0.001). The probability of urticaria in young patients was three times higher than in older patients (95% CI 1.863–4.994).

Drugs

The incidence of adverse reactions to different groups of drugs in three age groups did not differ significantly from the data of the entire sample (Fig. 3).

In group 1, 105 cases of reactions to drugs were detected, as well as 153 and 257 cases in group 2 and group 3, respectively.

In three groups, in terms of incidence of drug-induced reactions, antibiotics ranked first (20% in group 1; 19.61% in group 2; 18.68% in group 3), while nonsteroidal anti-inflammatory drugs (12.38% in group 1; 12.42% in group 2; 9.73% in group 3) and local anesthetics (11.43% in group 1; 14.38% in group 2; 10.51% in group 3) ranked second and third.

Group B vitamins ranked fourth in incidence in groups 2 and 3 (8.5% and 8.17%) and were superseded by non-narcotic analgesics (10.48%) in group 1. In groups 2 and 3, reactions to non-narcotic analgesics were less common in 1.96% and 3.5% of patients, respectively.

In the group 2, muscle relaxants ranked fifth in the incidence (5.23%). In group 3, these were angiotensin-converting enzyme inhibitors (ACE inhibitors) (5.84%), the reactions which were less common in groups 1 and 3, namely 0.95% and 2.61%, respectively.

Reactions to iodine-contrast drugs were registered with approximately equal frequency in all groups (0.95% in group 1; 1.96% in group 2; and 3.5% in group 3; Table 4).

When comparing the incidence of reactions to different groups of drugs in patients of three age groups, significant differences were revealed only in the category of ACE inhibitors in elderly and senile patients. Adverse reactions to ACE inhibitors in elderly and senile patients were noted in 15 (6%) cases, while in patients of other

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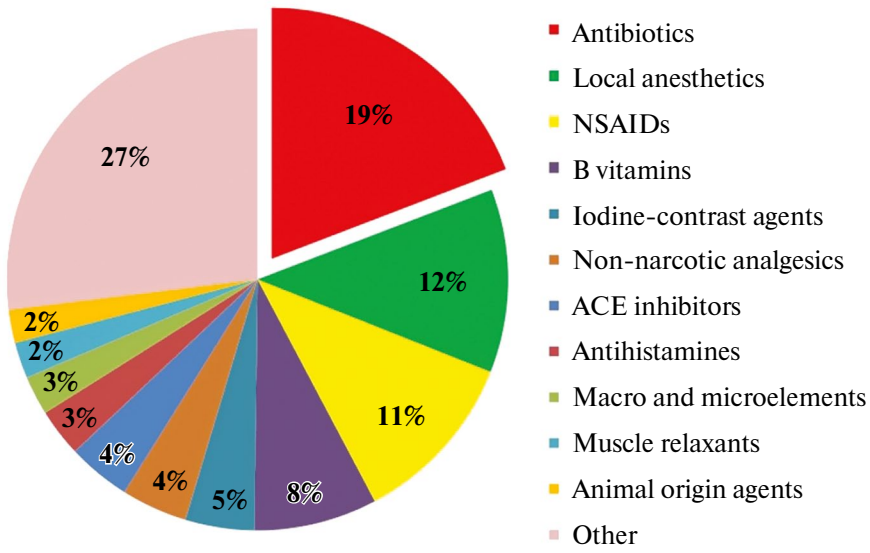

Fig. 3. Structure of the most frequently encountered groups of drugs in the whole sample, which caused hypersensitivity reactions
Note. НПВС — non-steroidal anti-inflammatory drugs; иАПФ — angiotensin converting enzyme inhibitors.

ages, they were recorded in 6 (2.3%) cases. The differences in indicators assessed using Pearson's chi-square test were statistically significant ($p = 0.044$). The probability of reactions to ACE inhibitors in elderly and senile patients was 2.6 times higher than in younger patients (95% CI 0.998–6.847).

Antibacterial drugs

Among antibiotics, in terms of incidence of drug-induced hypersensitivity reactions in all age groups, the leading positions were taken by drugs of the penicillin series (42.86% in the group 1; 50% in the group 2; 50% of the subjects in the group 3) and cephalosporins (28.57% in the group 1, 26.67% in the group 2, and 12.5% of patients in the group 3) (Fig. 4; Table 4). A similar distribution of antibiotic groups is noted in patients from the general sample (48.48% of penicillins and 20.2% of cephalosporins).

When comparing the clinical manifestations of drug-induced hypersensitivity to the penicillin and cephalosporin series antibiotics, no significant differences were revealed in patients of all age groups.

Angiotensin-converting enzyme inhibitors

For the entire sample, the incidence of adverse reactions to ACE inhibitors was 4.07% (Table 5), most of which (5.84%) were significantly detected in patients of age 3.

When comparing the clinical manifestations of reactions to ACE inhibitors in patients of all groups, no significant differences were found (Fig. 5), and 68% of all reactions to this group of drugs were represented by cough (side effect of ACE inhibitors). Angioneurotic edema was registered in three patients of group 2 (75%). Such reactions as urticaria, dermatitis, and anaphylactic shock have not been recorded.

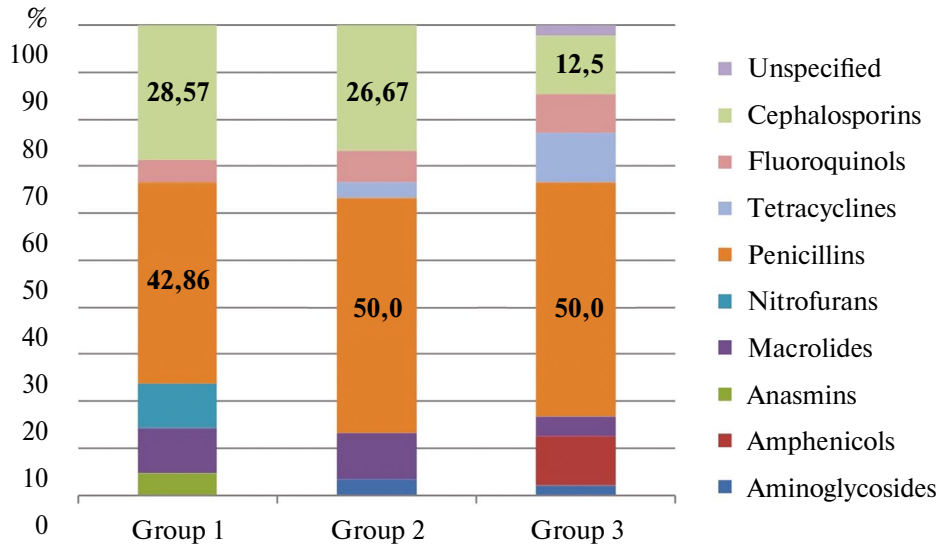

Fig. 4. Structure of clinical manifestations of drug intolerance to angiotensin-converting enzyme inhibitors in all groups.

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Table 4. Groups of drugs, which caused the most frequent drug hypersensitivity reactions in three age groups

Clinical and pharmacological group of the drugs	Incidence of drug intolerance reactions		
	Group 1 *n* = 105	Group 2 *n* = 153	Group 3 *n* = 257
Antibacterial drugs, *n* (%)	**21 (20)**	**30 (19.61)**	**48 (18.68)**
Aminoglycosides, *n*	0	1	1
Amphenicols, *n*	0	0	5
Anasmins, *n*	1	0	0
Macrolides, *n*	2	3	2
Nitrofurans, *n*	2	0	0
Penicillins, *n*	9	15	24
Tetracyclines, *n*	0	1	5
Fluoroquinolones, *n*	1	2	4
Cephalosporins, *n*	6	8	6
Unspecified, *n*	0	0	1
NSAIDs, *n* (%)	**13 (12.38)**	**19 (12.42)**	**26 (10.12)**
Combined NSAIDs, *n*	1	0	0
Local NSAIDs, *n*	0	0	1
NSAIDs (mainly COX-2/selective), *n*	2	7	6
NSAIDs (COX-1, 2 non-selective), *n*	10	10	17
Unspecified, *n*	0	2	2
Local anesthetics, *n* (%)	**12 (11.43)**	**22 (14.38)**	**27 (10.51)**
Amides, *n*	9	11	10
Paraamino group, *n*	3	11	17
Non-narcotic analgesics, *n* (%)	**11 (10.48)**	**3 (1.96)**	**8 (3.11)**
Combined with paracetamol, *n* (% of the group)	7	0	0
Metamizole sodium, *n*	4	2	7
Paracetamol, *n*	0	1	1
B vitamins, *n* (%)	**7 (6.67)**	**13 (8.5)**	**21 (8.17)**
Muscle relaxants, *n* (%)	**1 (0.95)**	**8 (5.23)**	**3 (1.17)**
Baclofen, *n*	0	0	1
Rocuronium, *n*	0	2	0
Suxamethonium chloride, *n*	0	1	0
Tizanidine, *n*	0	2	1
Tolperisone, *n*	1	3	1
ACE inhibitors, *n* (%)	**1 (0.95)**	**4 (2.61)**	**15 (5.84)**
Captopril, *n*	0	1	2
Lisinopril, *n*	0	0	3
Perindopril, *n*	1	2	3
Enalapril, *n*	1	0	7
Unspecified, *n*	0	1	0
Iodine-contrast agents, *n* (%)	**6 (5.72)**	**8 (5.23)**	**9 (3.5)**
Others, *n* (%)	**33 (31.42)**	**46 (30.06)**	**100 (38.9)**

Note. NSAIDs — Nonsteroidal anti-inflammatory drugs; COX — cyclooxygenase; ACE inhibitors — angiotensin-converting enzyme inhibitors.

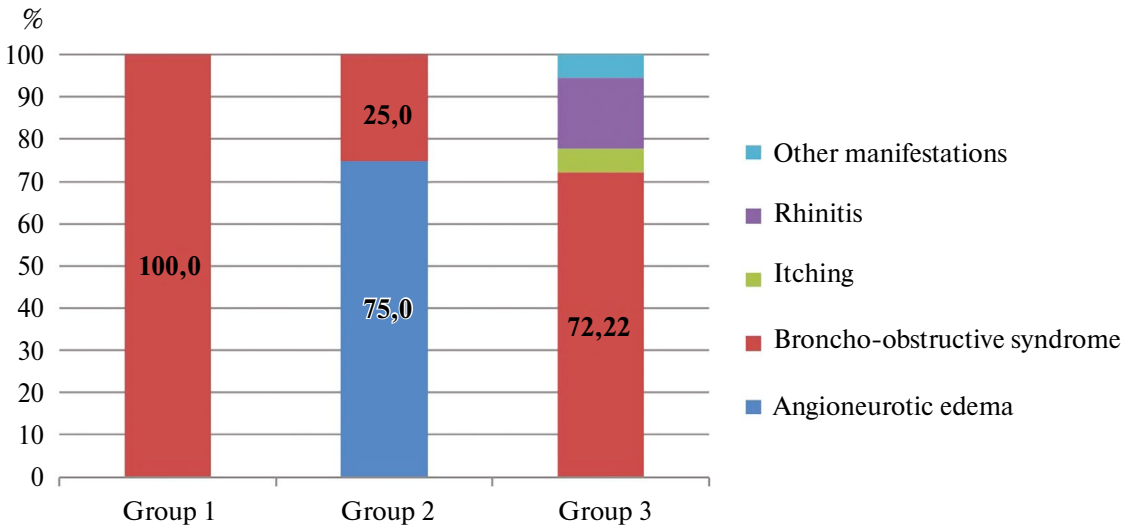

Fig. 5. Structure of clinical manifestations of drug intolerance to angiotensin-converting enzyme inhibitors in three age groups.

Somatic pathology and allergies

The presence of somatic pathology of three or more systems in combination with age did not show a meaningfully significant opportunity to increase the amount of drugs to which drug-induced hypersensitivity reactions may occur; also, this criterion did not aggravate the clinical manifestations of drug intolerance, as patients with drug-induced anaphylactic shock had both the somatic pathology of three or more systems and a less significant comorbid background. The presence of allergic pathology both separately and in combination with somatic pathology of three or more systems, both in older and younger patients also did not reveal a clinically significant increase in the severity and number of drug intolerance reactions.

Additional research outcomes

Clinical manifestations of adverse drug reactions

Clinical manifestations of drug reactions in all three groups were more often defined as angioneurotic edema (22.11%) and dermatitis (20.03%). Other reactions were less common, including other manifestations of drug reactions (16.93%), urticaria (14.68%), cough and choking (10.54%), anaphylactic shock (11.92%), itching (2.07%), and rhinitis (1.73%) (Fig. 6; Table 3).

Drugs

A total of 515 drugs were identified, which induced adverse reactions. Further, we distributed them into 33 groups according to the clinical and pharmacological classification. We selected 11 groups (in decreasing incidence) of them, which were antibiotics (19.19%), local anesthetics (11.82%), nonsteroidal anti-inflammatory

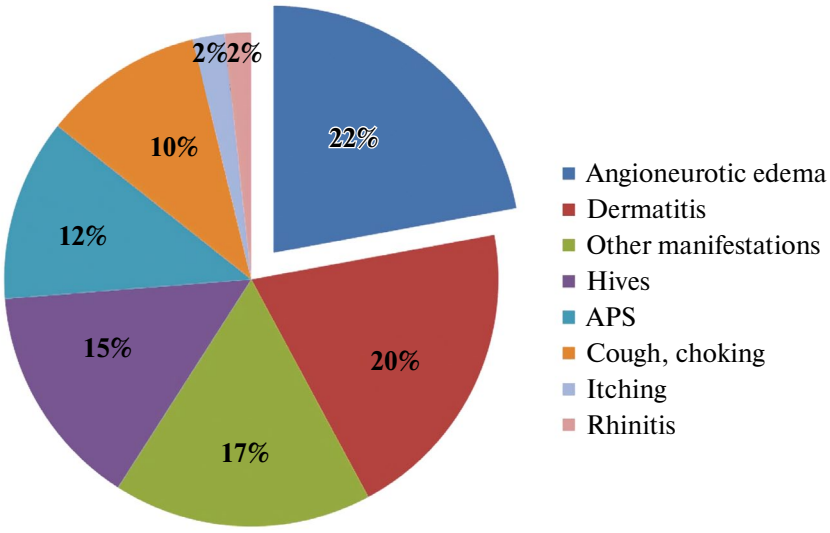

Fig. 6. The overall structure of clinical manifestations of drug reactions;
Note. АФШ — anaphylactic shock. This diagram does not include cough on angiotensin-converting enzyme inhibitors.

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Table 5. Groups of drugs for which drug hypersensitivity reactions occurred most frequently in the whole sample

Clinical and pharmacological group of the drug	Incidence of drug hypersensitivity reactions
Antibiotics, *n* (%)	99 (19.9)
Local anesthetics, *n* (%)	61 (11.82)
NSAIDs, *n* (%)	58(11.24)
B vitamins, *n* (%)	41 (7.95)
Iodine-contrast agents, *n* (%)	23 (4.46)
Non-narcotic analgesics, *n* (%)	22 (4.26)
Angiotensin-converting enzyme inhibitors, *n* (%)	21 (4.07)
Antihistamines, *n* (%)	16 (3.1)
Macro- and microelements, *n* (%)	13 (2.52)
Muscle relaxants, *n* (%)	12 (2.33)
Animal origin drugs, *n* (%)	11 (2.13)
Others, *n* (%)	139 (26.94)

Note. NSAIDs — nonsteroidal anti-inflammatory drugs.

drugs (11.24%), B vitamins (7.95%) , iodine preparations (4.46%), ACE inhibitors (4.07%), antihistamines (3.1%), macro and microelements (2.52%), muscle relaxants (2.33%), animal origin products (2.13%). The others (26.94%) included drugs whose incidence of reactions was less than 2% (Table 5; Fig. 3).

Antibacterial drugs

In the range of the clinical manifestations of drug-induced hypersensitivity to antibacterial drugs, reactions in the form of dermatitis (31.4%) and angioneurotic edema (23.14%) were most common in the general sample; while manifestations in the form of rhinitis were not recorded.

In the range of the most common hypersensitivity reactions to penicillins in the general sample, dermatitis (36.21%), angioneurotic edema (20.69%), and urticaria (20.69%) were identified. On the other hand, hypersensitivity reactions to cephalosporins differed and manifested as anaphylactic shock (40%), angioneurotic edema (28%), and urticaria (12%).

Adverse events

During the study, no adverse events were registered.

Discussion

Summary of the main research outcome

The patient's age does not affect the possibility of reactions to certain groups of drugs (except for ACE inhibitors, which was most likely due to the higher frequency of prescribing antihypertensive therapy in patients of this age group). Aggravation of clinical manifestations and the occurrence of polypragmasy are not associated with age or comorbid background. The correlation dependence between age and non-life-threatening clinical manifestations of drug-induced hypersensitivity indicates the absence of a significant effect of age on the possibility of anaphylactic shock or angioneurotic edema.

A high percentage of identified reactions to local anesthetics was associated to a greater extent with vasovagal reactions (33.87% of patients noted reactions in the form of fainting or precollaptoid state) than with hypersensitivity reactions.

Most of the reactions, in the form of anaphylactic shock, were not documented, and the patient could misinterpret the condition that arose, which could affect the results.

Research limitations

Pharmacological and allergic history data were indicated only based on the information received from the patient and, possibly, a diagnosis of drug-induced hypersensitivity previously made in another healthcare facility. Furthermore, when planning and conducting the study, the sample size was not calculated to achieve the required statistical power of the results. In this regard, the sample of participants obtained during the study cannot be considered sufficiently representative, which does not enable extrapolating the results obtained and their interpretation (conclusions) to the general population of similar patients beyond the study.

Conclusion

The influence of age as a risk factor for the development of drug-induced hypersensitivity is not completely understood. According to our data, in all patients, regardless of age, adverse reactions occurred with approximately the same frequency to antibiotics, nonsteroidal anti-inflammatory drugs, local anesthetics, B vitamins, non-narcotic analgesics, which indicates that age does not influence the risk of reactions to certain groups of drugs. The revealed significant differences in ACE inhibitors are associated with the high frequency and duration of their use by elderly and senile people. Elderly patients also have some aspects of the clinical manifestations of adverse reactions to drugs, which may be associated with the presence of combined comorbid conditions and the peculiarities of their therapeutic correction. Such pa-

tients require more careful attention from primary care physicians when prescribing therapy to avoid possible cross-effects of a number of drugs.

Additional information

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