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INVESTIGATION OF MEDICALLY INDUCED SKIN REACTIONS BASED ON THE ANALYSIS OF REPORTS OF ADVERSE DRUG REACTIONS IN THE REPUBLIC OF CRIMEA (FROM 2009 TO 2016)

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Drug hypersensitivity reactions are among the most important problems that arise when using drugs. The occurrence of such reactions in the population is at least 7% and tends to a constant increase. The most frequent manifestations of drug hypersensitivity reactions are medically induced skin lesions. ***The aim*** *of this research was to study and analyze the cases of development of skin drug reactions on the basis of the reports on the adverse reactions (ADRs) of the drugs, registered in the Republic of Crimea in the period from 2009 to 2016.* ***Materials and methods.*** *The objects of the research were report cards about the adverse reactions, registered in the regional base (registry) of spontaneous messages called ARCADe (Adverse Reactions in Crimea, Autonomic Database) for the period from 2009 to 2016. During the analysis of the report cards, 2,698 cases of the development of skin drug reactions arising in response to the use of drugs in patients were selected. The study of the frequency of occurrence of skin drug reactions in the application of various groups of drugs was carried out taking into account the codes of the Anatomical Therapeutic Chemical (ATC) Classification System of drugs of the World Health Organization (WHO).* ***Results.*** *Of the study showed that the development of skin drug reactions was most often associated with the use of antimicrobial agents for internal use, nonsteroidal anti-inflammatory drugs (NSAIDs), drugs for the treatment of diseases of the gastrointestinal tract and agents that affect the nervous system. Among the clinical manifestations of skin drug reactions, generalized and localized rashes prevailed, and itching and hyperemia of the skin were much less common in patients. The analysis of age categories showed that the most frequently medically induced reactions occurred in children from birth to 3 years, as well as in the age group of patients from 46 to 60 years. The risk factors identified in the course of the analysis, were female gender, early childhood and old age, as well as the presence of aggravated drug allergy history.* ***Conclusion.*** *Drug hypersensitivity reactions create certain difficulties in clinical practice related to the diagnosis, treatment and prophylaxis, and may also cause danger to health or life of patients. In this connection, the study of such adverse reactions is the most important task of practical health care and requires direct participation of doctors of all specialties.*

Keywords: *medicines, adverse reactions, drug hypersensitivity, medicinal skin lesions*

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ИЗУЧЕНИЕ ЛЕКАРСТВЕННО-ИНДУЦИРОВАННЫХ КОЖНЫХ РЕАКЦИЙ НА ОСНОВАНИИ АНАЛИЗА КАРТ-ИЗВЕЩЕНИЙ О НЕЖЕЛАТЕЛЬНЫХ РЕАКЦИЯХ ЛЕКАРСТВЕННЫХ СРЕДСТВ В РЕСПУБЛИКЕ КРЫМ ЗА 2009–2016 ГГ.

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Реакции лекарственной гиперчувствительности (РЛГ) являются одними из наиболее важных проблем, возникающих при применении лекарственных препаратов. Встречаемость подобных реакций в популяции составляет не менее 7% и имеет тенденцию к постоянному росту. Наиболее частыми проявлениями РЛГ являются лекарственно-индуцированные поражения кожи. ***Целью настоящего исследования*** *явилось изучение и анализ случаев развития кожных лекарственных реакций (КЛР) на основании карт-извещений о нежелательных реакциях (НР) лекарственных средств (ЛС), зарегистрированных в Республике Крым за 2009–2016 гг.* ***Материалы и методы.*** *В работе были использованы данные карт-извещений о НР ЛС, зарегистрированных в региональной базе (реестре) спонтанных сообщений ARCADe (Adverse Reactions in Crimea, Autonomic Database) за период 2009–2016 гг. При проведении анализа карт-извещений было отобрано 2698 случаев развития КЛР, возникающих в ответ на применение у пациентов лекарственных препаратов. Изучение частоты встречаемости КЛР при применении различных групп ЛС проводилось с учетом кодов Анатомо-терапевтически-химической (АТХ) классификации лекарственных средств Всемирной Организации Здравоохранения (ВОЗ).* ***Результаты.*** *Развитие кожных лекарственных реакций наиболее часто было связано с применением противомикробных средств для внутреннего применения, нестероидных противовоспалительных средств (НПВС), препаратов для лечения заболеваний желудочно-кишечного тракта и средств, влияющих на нервную систему. Среди клинических проявлений кожных лекарственных реакций преобладали генерализованные и локализованные сыпи, значительно реже у пациентов наблюдались зуд и гиперемия кожных покровов. Анализ возрастных категорий показал, что наиболее часто лекарственно-индуцированные реакции возникали у детей с рождения до 3 лет, а также в возрастной группе пациентов от 46 до 60 лет. Выявленными в ходе проведения анализа факторами риска развития КЛР были женский пол, ранний детский и пожилой возраст, а также наличие у пациентов отягощенного лекарственного аллергологического анамнеза.* ***Заключение.*** *Реакции лекарственной гиперчувствительности создают определенные трудности в клинической практике, связанные с их диагностикой, лечением и профилактикой, а также могут представлять собой угрозу здоровью и жизни пациентов. В связи с чем, изучение таких НР является важнейшей задачей практического здравоохранения и требует непосредственного участия врачей всех специальностей.*

Ключевые слова: *лекарственные средства, нежелательные реакции, лекарственная гиперчувствительность, лекарственные поражения кожи*

INTRODUCTION

Drug hypersensitivity reactions are among the most important problems that arise when drugs are used. The frequency of such reactions in the population is about 7% and tends to a constant increase [1, 2]. Clinical manifestations of drug hypersensitivity reactions are allergic reactions of varying severity, which can occur directly to active ingredients or to auxiliary components of the drug [3, 4].

The most frequent manifestations of drug hypersensitivity reactions are medically induced skin lesions. According to the terminology worked out by the World Health Organization, a medically induced skin reaction is defined as any unintended and harmful morphological skin change that occurred during systemic or local use of the drug in usual doses for the purpose of prevention, treatment and diagnosis [4]. According to the literature data, the frequency of occurrence of such reactions is in the range of 2–3% in hospitalized patients [5], and among all detected adverse drug reaction (ADR) – from 19 to 48% [6,7]. At the same time, the relevance of studying skin drug reactions is caused not only by the high frequency of their development, but also by the severity and unpredictability of such reactions, which can cause a significant danger to health or life of patients.

THE AIM of this investigation was to study and analyze the cases of development of skin drug reactions on the basis of report cards of ADRs to the drugs regis-

tered in the Republic of Crimea in the period from 2009 to 2016, the identification of pharmacological groups of the drugs that cause skin drug reactions most often, and also the allocation of risk factors for the development of such adverse reactions.

MATERIALS AND METHODS

The objects of the research were the report cards about the adverse reactions, registered in the regional base (registry) of spontaneous messages called ARCADe (Adverse Reactions in Crimea, Autonomic Database) for the period from 2009 to 2016. When analyzing the report cards, 2,698 cases of development of skin drug reactions were selected in response to the use of drugs in patients. The criterion for the selection of cases of ADR was an indication of the skin manifestations of ADRs in the section "Standardized description of the reaction".

The study of the frequency of occurrence of skin drug reactions in the application of various groups of drugs was carried out taking into account the codes of the Anatomical Therapeutic Chemical (ATC) Classification System of drugs of the World Health Organization (WHO) [8].

The research methodology (the analysis of the registry data) did not imply making comparisons and determining the data correlations among themselves. ADRs frequency determination was performed in MS Excel 2016 Microsoft Office.

RESULTS AND DISCUSSION

For the analysis of cases of skin drug reactions arising in response to the use of different groups of drugs, 2,698 report cards were selected from the regional database – ARCADe – of spontaneous messages, which accounted for 43.1% of the total number of the registered ADRs for the corresponding period (6254 report cards).

The first stage of the research was to study the frequency of cases of the development of skin drug reactions when using drugs of different pharmacological groups. The analysis of the report cards showed that the most frequent skin drug reactions occurred when using drugs of the group of antimicrobial agents for systemic use (1215 cases), which accounted for 45% of the total number of medically induced skin reactions. Such adverse reactions occurred much less often when using drugs that affect the digestive system and metabolism (277 cases, 10.27%), drugs that affect the nervous system (239 cases, 8.85%), and drugs that affect the musculoskeletal systems, including nonsteroidal anti-inflammatory drugs (NSAIDs) (229 cases, 8.49%). The frequency of occurrence of skin drug reactions when using drugs of other pharmacotherapeutic groups in accordance with the WHO Anatomic Therapeutic Chemical Classification of Drugs is presented in Fig. 1.

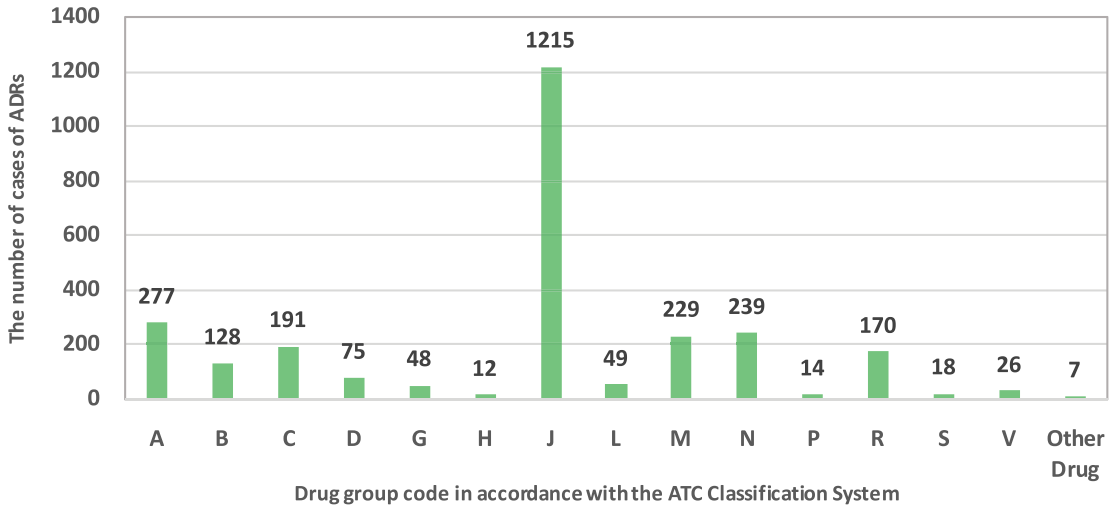

Figure 1. Distribution of drugs causing skin drug reactions, in accordance with the WHO ATC Classification System of Drugs

Studying the frequency of adverse reactions to individual groups of drugs that cause medically induced skin reactions showed that among the group of antibacterials for systemic use, such adverse reactions were most often associated with the use of J01 group (antibacterials for systemic use) – 1065 cases (87, 65% of the total number

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of cases of adverse reactions in this group). Less commonly, skin drug reactions were associated with the use of antivirals for systemic use (J05 – 72 cases, 5.9%) and antimycobacterials (J04 – 43 cases, 3.54%) (Fig. 2).

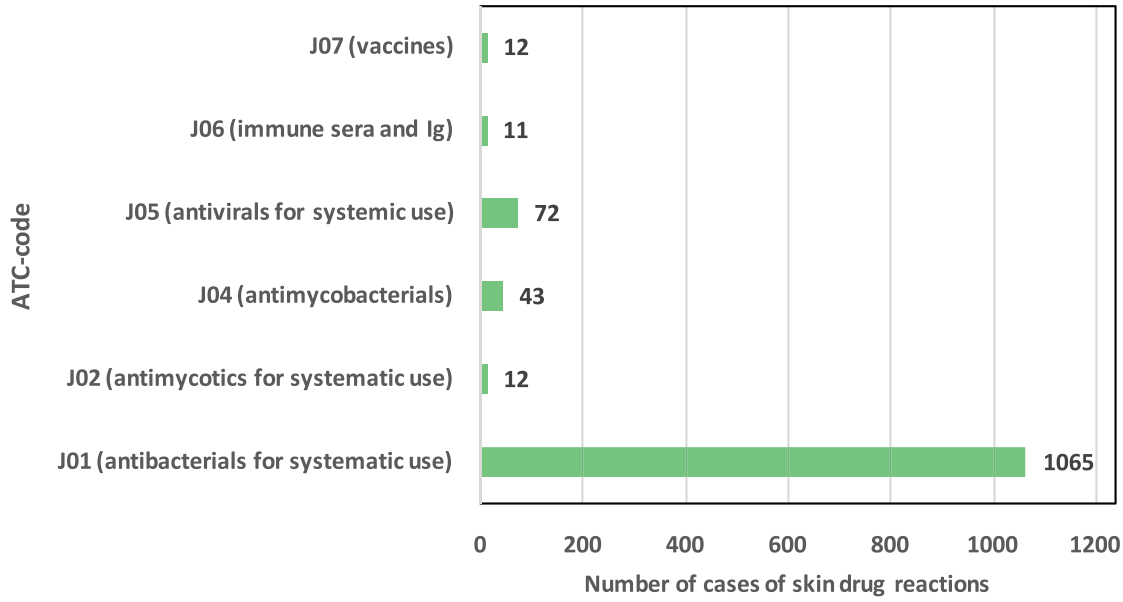

Figure 2. Distribution of cases of skin drug reactions in the group of antibacterials for systemic use

The analysis of skin drug reactions of individual groups for system use, confirms the known data on the high incidence of allergic reactions when using antibacterial drugs, including β-lactam antibiotics of the cephalosporins and penicillins groups [9–11]. In our case, the frequency of development of skin drug reactions when using these groups of drugs was 557 (52.3% of the total number of cases of adverse reactions to antimicrobial agents) and 207 cases (19.4%), respectively. The frequency of occurrence of drug-induced skin reactions of individual members of the β-lactamantibiotic groups is presented in Table 1. Other groups of antimicrobial agents caused allergic reactions much less frequently: fluoroquinolones – 122 cases of ADRs (11.5%), macrolides and azalides – 65 cases (6.1%), aminoglycosides – 40 cases (3.8%). Levofloxacin (45 cases of ADRs) and Ciprofloxacin (42 cases) became the "leaders" in the development of drug-induced reactions in the group of fluoroquinolones. In the group of Macrolide antibiotics, the development of skin drug reactions was most frequently recorded with Azithromycin (34 cases of ADRs) and Clarithromycin (13 cases). The high incidence of development of skin drug reactions in the above mentioned groups of drugs is most likely due to their frequent prescription by health care professionals, as well as the use of drug data by patients during self-treatment. [12].

The greatest number of cases of skin drug reactions in the use of antiviral drugs was caused by the use of drugs effective against HIV (non-nucleoside reverse transcriptase inhibitors (NNRTI) – 28 cases of ADRs, nucleoside reverse transcriptase inhibitors (NRTI) – 6 cases, protease inhibitors – 4 cases). Combined antiviral drugs that are effective against HIV, caused the development of ADRs in 9 cases.

Table 1. Frequency of occurrence of drug-induced skin reactions when using drugs of the ß-lactam antibiotics group (penicillins, cephalosporins)

Representatives of antimicrobial groups	The number of cases of skin drug reactions, the absolute value	The number of cases of skin drug reactions,% (relative to the total number of cases of skin drug reactions)
Penicillins		
Ampicillin (J01CA01)	5	0.2%
Amoxicillin (J01CA04)	72	2.7%
Benzylpenicillin (J01CE01)	4	0.15%
Ampicillinandbeta-lactamaseinhibitor (J01CR01)	15	0.6%
Amoxicillinandbeta-lactamaseinhibitor (J01CR02)	111	**4.1%**
Cephalosporins		
First-generation		
Cefalexin (J01DB01)	14	0.5%
Cefazolin (J01DB04)	13	0.48%
Second-generation		
Cefuroxime **(**J01DC02)	53	2%
Third-generation		
Cefotaxime (J01DD01)	152	**5.6%**
Ceftazidime (J01DD02)	12	0.4%
Ceftriaxone (J01DD04)	230	**8.5%**
Cefixime (J01DD08)	33	1.2%
Cefoperazone (J01DD12)	5	0.18%
Cefpodoxime (J01DD13)	16	0.6%
Ceftibuten (J01DD14)	1	0.04%
Ceftriaxone, combinations (J01DD54)	6	0.2%
Cefoperazone and beta-lactamase inhibitor (J01DD62)	9	0.3%
Fourth-generation		
Cefepime (J01DE01)	8	0.3%

Among the anti-TB drugs, the development of medically induced skin reactions in most cases (28 cases, 65% of the total number of cases for anti-TB drugs) was associated with the use of Pyrazinamide. Much less frequently, skin drug reactions occurred with the use of Isoniazid, Ethambutol and Rifampicin.

Special attention should be paid to the high incidence of medically induced skin reactions that occur when using NSAIDs (186 cases, which accounted for 6.9% of the total number of cases of skin drug reactions). In this pharmacological group, the most frequently similar ADRs were associated with the use of drugs derived from Propionic acid (106 cases) and Acetic acid (51 cases). Analysis of the frequency of skin drug reactions in the application of individual representatives of the groups of NSAIDs is presented in Fig. 3.

The largest number of skin drug reactions was registered with the use of Ibuprofen (99 cases, 53.22%), Diclofenac (31 cases, 16.7%), Ketorolac (18 cases, 9.7%) and Nimesulide (12 cases, 6.45 %).

The study of drug-producing countries that cause skin drug reactions revealed that in 911 cases the development of ADRs was associated with the use of drugs manufactured in Ukraine, in 309 cases in the territory of the Russian Federation. The development of ADRs against the background of the use of drugs produced by foreign pharmaceutical companies was observed slightly less. Thus, drugs produced in India caused 291 cases of skin drug reactions, in the UK –210 cases, in Germany – 177 cases of ADRs.

A study of the clinical manifestations of medically induced skin reactions showed that the most common forms were: generalized skin rashes (1673 cases of ADRs, 62%), localized skin rashes (713 cases of ADRs, 26.4%), localized and generalized skin itching (128 and 95 cases of ADRs, respectively), as well as skin redness (78 cases, 2.9%). Indicators of the occurrence of such manifestations in patients are presented in Table 2.

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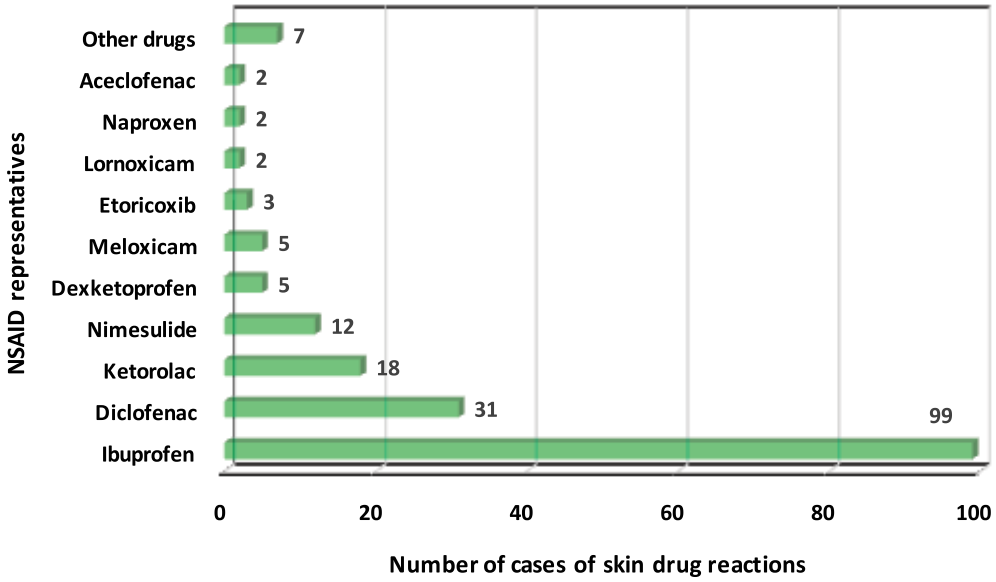

Figure 3. Frequency of skin drug reactions when using NSAIDs

Table 2. Frequency of various clinical manifestations of skin drug reactions

Clinical manifestations of skin drug reactions	Number of reported cases of ADRs	
	Number	%
Generalized rash	1673	62
Localized rash	713	26.4
Generalized pruritus	95	3.5
Localized pruritus	128	4.8
Skin hyperemia	78	2.9
Allergic toxic dermatitis	9	0.3
Photodermatitis	2	0.1

The analysis of the age periods for which the occurrence of ADRs in the form of skin manifestations was typical, showed the following results (Fig.4): the most frequent complications of pharmacotherapy were observed before the age of 3 years – 766 cases (from birth to 28 days – 42 cases of ADRs, 28 days – 1 year – 392 cases of ADRs, from 1 to 3 years – 342 cases) and in the age category «46-60 years» – 441 cases. It is worth noting that a rather high incidence of skin drug reactions was observed in the age periods of "19–30 years", "31–45 years" and "61–75 years" – 349, 354 and 331 cases of ADRs, respectively.

A study of the gender of the patients revealed that the most frequent skin drug reaction occurred in females – 1613 (60%) cases, in the remaining 1085 cases ADRs (40%) was observed in males.

Our further analysis was aimed at studying the routes of administration of drugs that cause medically induced skin reactions. So, the most frequent way of administering such drugs was their ingestion (per os) – 1326 cases (49.15%), less often ADRs occurred against the background of parenteral administration of drugs: intramuscularly – 535 cases (19.8%), intravenously – 510 cases (18.9%), subcutaneously – 32 cases (1.19%). Attention is drawn to the fact that in 139 cases (5.15%) skin drug reactions occurred with the external use of drugs, and in 52 cases (1.9%) with rectal administration.

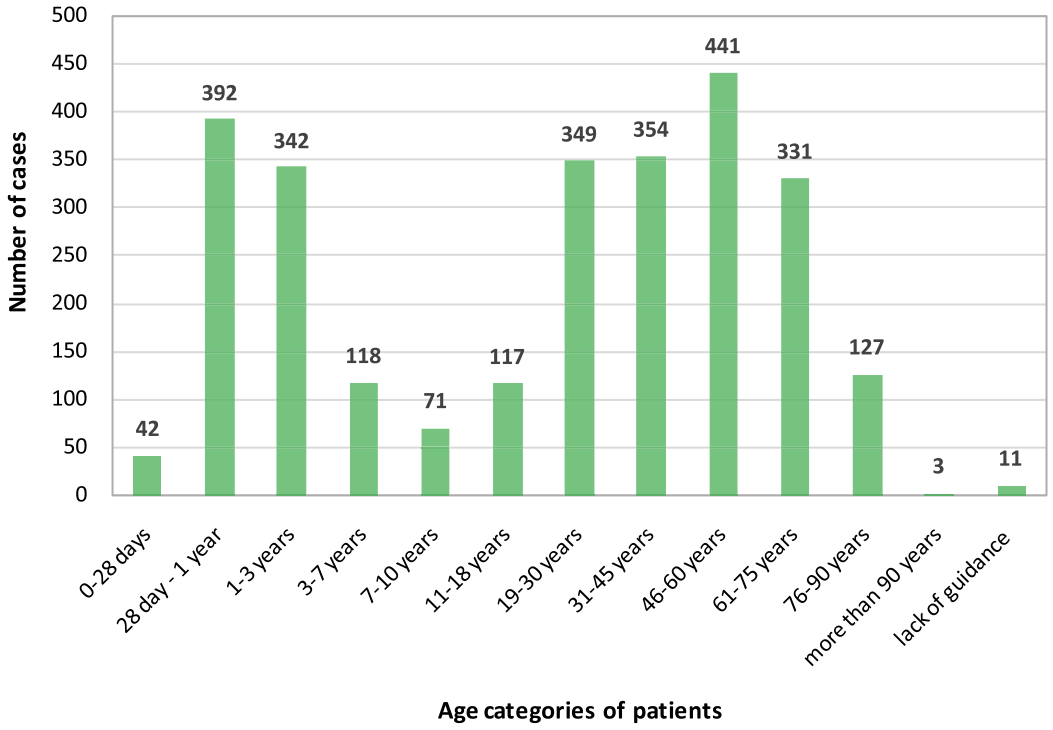

Figure 4. Distribution of patients with medically induced skin reactions by age

One of the most important factors determining the likelihood of adverse reactions of an allergic nature is the patient's history of hypersensitivity to drugs, food components, contact home allergens and other factors. A study of the allergic history in patients with skin drug reactions showed that in most cases it was calm (2399 cases, 88.92%), while in the other cases an aggravated allergic history was observed: drug allergy – 156 cases of ADRs (5.8%), food allergy – 80 cases of ADRs (3%), household (contact allergy) – 35 cases (1.3%), in 28 cases patients had mixed allergies (Fig. 5).

In addition, one of the significant factors necessary for assessing the cause-effect relationship between taking a suspected drug and the skin drug reaction that occurs is the number of drugs prescribed simultaneously with it. In our case, the frequency of polypragmasy (simultaneous administration of 5 or more drugs) amounted to 320 cases of development of a skin drug reaction. At the same time, simultaneous prescription of 4 drugs was observed in 162 cases (6%), 5 drugs – in 83 cases (3.1%), 6 drugs – in 40 cases (1.5%). The prescription of 7 or more drugs was observed in 35 cases, which could significantly increase the risk of adverse reactions (*Fig*. 6).

The course of immediate-type allergic reactions, the appearance of affected skin lesions are characterized by a high rate of development and unpredictability. In this respect, treatment is reduced, as a rule, to the abolition of the drug that caused an adverse reaction, and to the conduct of symptomatic therapy. The analysis of cases of skin drug reactions in the Republic of Crimea showed that the cancellation of suspected drugs was carried out in 2651 cases (98.26%), hereby in 2266 cases the cancellation of the suspected drug was accompanied by the disappearance of adverse reactions.

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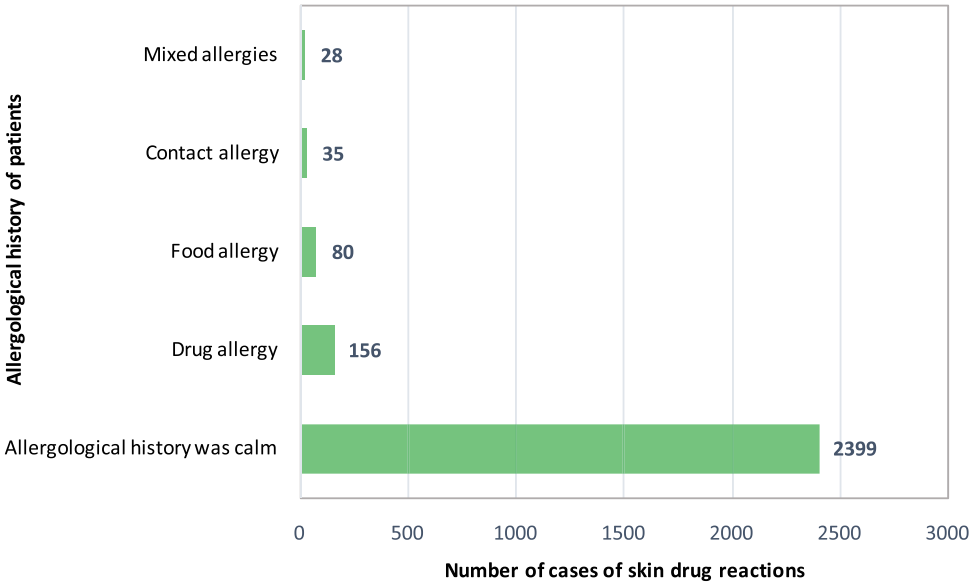

Figure 5. Analysis of the allergological history of patients with manifestations of skin drug reactions

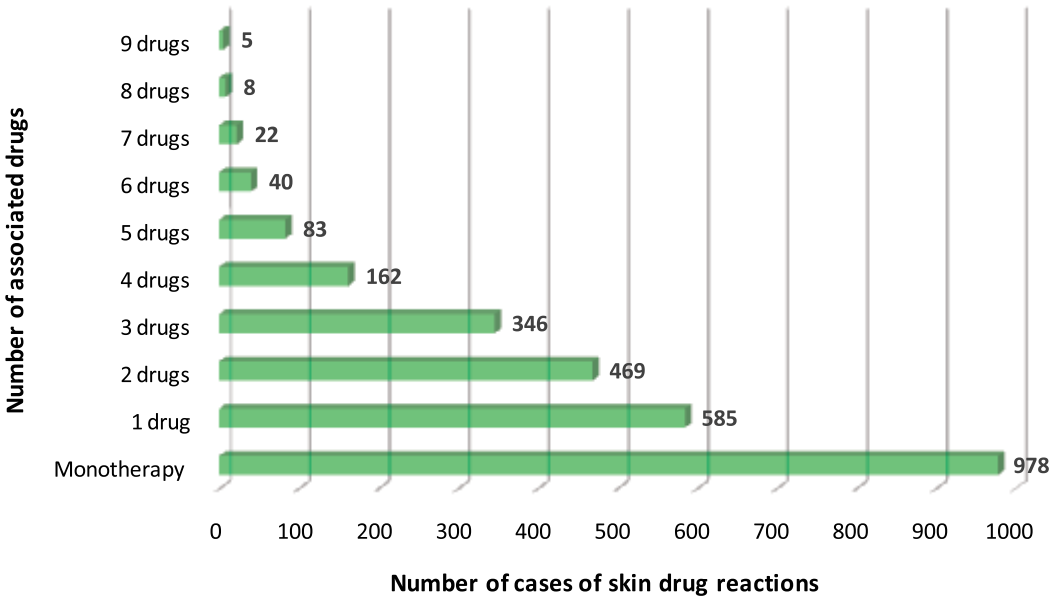

Figure 6. Analysis of report cards with manifestations of skin drug reactions by the number of associated drugs

Symptomatic therapy for the relief of skin drug reactions was observed in 2242 cases (83.1%), in other cases the patient did not need any additional pharmacotherapy.

The next stage of the study of skin drug reactions was aimed at analyzing the outcome of undesirable drug reactions. The results of the analysis showed that in most cases, skin drug reactions were not serious and did not cause pronounced consequences for patients (2009 cases, 74.5%). However, it is worth noting the frequency of serious consequences of ADRs for patients:

a life-threatening condition was observed in 32 cases (1.19%), hospitalization and extension of hospitalization of the patient's terms were required in 261 (9.7%) and 153 cases (5.7%) respectively. In 242 cases, the development of a skin drug reaction led to the patient's temporary disability (9%).

Thus, the results obtained during the analysis confirmed a high frequency of occurrence, severity and unpredictability of the occurrence of drug-induced skin reactions [13, 14]. Among all pharmacological groups of drugs, the most frequent skin drug reactions were associated with the use of antibacterials for systemic use, namely drugs of the cephalosporins and penicillins groups. Such high rates of development of ADRs when using these groups of drugs, could be associated not only with the presence of a β-lactam ring in their structure, which can covalently bind to serum proteins and the cell wall and cause the development of allergic reactions, but also with a significant frequency in clinical practice [15]. The risk factors for the development of skin drug reactions identified in the course of the analysis, were female gender (60% of cases), early childhood and old age, as well as the presence of burdened drug allergological history in patients.

CONCLUSION

At present, one of the priorities of the health care system is to monitor the effectiveness, safety and quality of drugs used in the stages of diagnosis, prevention and treatment of patients.

Sufficient knowledge of health professionals in the field of pharmacological safety of drugs will allow them not only to be prepared for the relief of serious unforeseen manifestations of skin drug reactions in the shortest possible time, but also to the possible prevention of life-threatening conditions associated with the use of drugs.

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Conflict of interest

The authors declare no conflict of interest.

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