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Allergy clinic patients' drug hypersensitivity

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Abstract

Background: Drug hypersensitivity reaction (DHR) is a common reason for an allergology consultation, during which it is not only necessary to gather a thorough medical history, but also to propose and perform diagnostic tests.

Objectives: The aim of the study was to retrospectively assess the patients with a profile of preliminary drug hypersensitivity diagnosis, the usefulness of NSAID hypersensitivity classification in outpatient practice, and to analyze the results of skin, provocation, and drug tolerance tests performed in Immunology and Allergy Clinic patients.

Methods: Around 501 medical records of patients referred to the academic allergy outpatient clinic from 2011 to 2019, and had a preliminary drug hypersensitivity diagnosis were analyzed. The diagnostic and drug tolerance tests results carried out in 269 patients of the Clinic from 2009 to 2019 were then evaluated.

Results: Among the patients referred due to suspected drug hypersensitivity, the majority (n=338, 67.5%) were believed to be hypersensitive to NSAIDs and antibiotics (n=272, 54.3%). In patients with hypersensitivity to NSAIDs, the mixed pattern was the most prevalent (n=73, 21.6%), followed by NECD (n=64, 18.9%) and NIUA (n=55, 16.3%). The second most common drug causing DHR were the antibiotics, mainly β -lactams (n=160, 58.8%), followed by macrolides (n=35, 12.9%). In hypersensitivity caused due to β -lactams, the delayed form was predominant (n=24, 15%) with manifested skin symptoms (n=74, 46.3%). Non-steroidal anti-inflammatory drugs (n=21, 42.9%), followed by antibiotics (n=11, 22.5%) were the commonest causes of anaphylaxis, as reported by 49 patients.

Conclusion: The study shows that a majority of patients with suspected drug hypersensitivity can be classified under the hypersensitivity umbrella based on their medical history, which is the basis for further diagnostic process.

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Introduction

Drug-related adverse reactions, including hypersensitivity reactions (HSR), is a significant clinical problem, most often requiring specialist consultation for accurate diagnosis. It is estimated that adverse drug reactions affect 10 to 19% of hospitalized patients, and between 3 and 6% of hospitalizations are caused by them.^{1,2} In outpatient care, the frequency of reported adverse drug reactions can reach up to 15%.^{3,4} The overall risk of HSR to most drugs ranges from 1 to 3%.^{5,6} According to the classical pharmacological classification of adverse drug reactions,⁷ we can divide them into two categories: (A) dose dependent and predictable reactions, and (B) dose independent and unpredictable reactions. The latest classification proposed by E. Phillips⁸ questions some of the current division principles, distinguishing the reactions related to the main mechanism of drug action (“on-target”) and associated additional drug interaction (“off-target”).

The most adverse reactions belong to type A, and only about 10-15% to type B, which is known as hypersensitivity. According to the EAACI/WAO nomenclature, the term drug allergy refers to hypersensitivity in which defined immune mechanisms are involved, both IgE-dependent and T-cell dependent. HSR that are clinically reminiscent of allergy, but for which it has not been a proven immune mechanism, should be classified as non-immunological.^{9,10}

Many patients who have a history of DHR are diagnosed without verifying tests.^{11,12} This may be due to the fact that the diagnostic process is difficult, and in most cases no in-vitro tests are available, and challenging procedures may be at risk of side effects.¹³ In addition, the immune mechanisms that cause drug allergies may expire over time, which may cause false negative results. Therefore, in routine practice, especially non-allergic, the diagnosis of drug hypersensitivity is usually based solely on history. DHR are most often caused by non-steroidal anti-inflammatory drugs (NSAIDs) and β -lactams (β L) antibiotics. These two types of hypersensitivity are caused by various mechanisms, and in each of them one can distinguish the sub-types (sub-phenotypes)¹⁵⁻¹⁶ which is a serious challenge for clinicians as misdiagnosis (the problem of over-diagnosis), as well as the lack of diagnosis in this case can have serious clinical implications.¹⁷

The aim of the study was to retrospectively assess the profile of the patients at the Immunology and Allergy Clinic, Medical University of Lodz, Poland referred for DHR, and to assess the usefulness of EAACI classification of hypersensitivity to NSAIDs and antibiotics in outpatient practice. In the second stage of the study, the results of diagnostic tests and drug tolerance tests performed on patients of the Immunology and Allergy Clinic were analyzed.

Materials and methods

An electronic database of the allergology consultancy from 2011 to 2019, of the Immunology and Allergy Clinic, the Central Clinical Hospital of the Medical University in Łódź containing patient disease histories with a preliminary diagnosis suggesting hypersensitivity to drugs, was analyzed. The ICD-10 codes used in the search of the general electronic database were as follows: Z88, i.e., an adverse reaction after medication in the history, T88.7 - unspecified, adverse effect of drugs

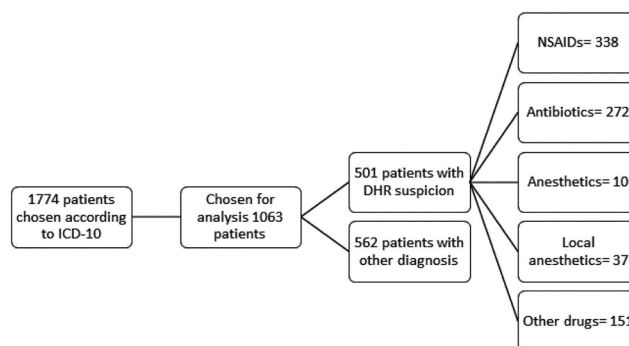


Figure 1 Test design. NSAIDs - non-steroidal anti-inflammatory drugs; DHR - drug hypersensitivity reaction.

Table 1 Demographic information about the patients.

Female n/N (%)	381/501 (76%)
Age, years (Mean \pm SD)	47.4 \pm 18.8

and medicinal products, T78 - negative effects, not classified elsewhere, and L27.0 and L27.1 - generalized and limited skin rash induced by drugs and other therapeutic agents. The search resulted in 1774 records, of which the first 1063 were selected for analysis. Of the selected group, 501 people were suspected of being hypersensitive to medications, as posed by an allergist doctor on the basis of an interview during the first visit. The rest of the 562 patients were diagnosed with other diseases (such as allergic rhinitis and conjunctivitis, food hypersensitivity or hymenoptera venom). These patients were excluded from further analysis. The study scheme is shown in [Figure 1](#). Demographic information about the study subjects is presented in the [Table 1](#). Hypersensitivity to NSAIDs was classified according to the division proposed by Kowalski et al.,²² among which there are: N-ERD (respiratory disease exacerbated by NSAIDs), NIUA (urticaria or angioedema triggered by NSAIDs), NECD (skin disease exacerbated by NSAIDs), SNIUA (urticaria, angioedema or anaphylaxis caused by a single NSAID), and SNIDR (delayed type reaction induced by a single NSAID).

According to Demoly P et al.⁵ drug hypersensitivity reactions were divided into immediate (less than one hour after drug intake), late (1-24 hours), and delayed (more than 24 hours) reactions.

Anaphylaxis was diagnosed according to EAACI definition - severe, potentially life-threatening systemic hypersensitivity reaction, characterized rapid onset of life-threatening blockage of airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.¹⁸

Drug hypersensitivity reactions are objectively reproducible symptoms or signs initiated by exposure to a drug at a dose normally tolerated by non-hypersensitive persons.¹⁹

In the second stage of the study, the medical records and results of skin tests and/or provocation tests with drugs, as well as drug tolerance tests performed from 2009-2020 were analyzed.

Table 2 Drugs that caused hypersensitivity symptoms reported by patients.

Drugs	n/N (%)
NSAIDs	338/501 (67.5%)
Antibiotics	272/501 (54.3%)
Local anesthetics	37/501 (7.4%)
Anesthetics	10 (2.0%)
	151/501 (30.1%)
antihypertensive drugs	23/501 (4.6%)
dietary supplements	16/501 (3.2%)
contrast agents	12/501 (2.4%)
Other drugs	
antihistamines	14/501 (2.8%)
tolperisone	9/501 (1.8%)
GCS	9/501 (1.8%)
other unknown	68/501 (13.6%)

NSAIDs - non-steroidal anti-inflammatory drugs; GCS - glucocorticoids

Statistics

The Chi2 test was used to compare the qualitative data. For the analysis, Statistica 13.1 (TIBCO Software Inc., USA) was used.

Results

Drugs that cause hypersensitivity reactions

Among 501 patients with suspected DHR, most patients $n=338$ (67.5%) reported hypersensitivity to NSAIDs, followed by antibiotics $n=272$ (54.3%). The symptoms of hypersensitivity to local anesthetics were shown in 37 (7.4%) people, general anesthetics in 10 (2%), and other drugs in 151 patients (30.1%). The symptoms caused by drugs from more than one group were reported by 129 people (25.8%). A detailed list of drugs causing hypersensitivity is presented in [Table 2](#).

Clinical phenotypes of NSAID hypersensitivity

Based on the analysis of 338 patients reporting NSAID DHR, in 266 patients (78.7%) one of the phenotypes could be determined. In the remaining 72 patients (21.3%), based on the available documentation (inaccurate description as the patient was unable to provide complete details), the form of hypersensitivity could not be determined. The distribution of hypersensitivity phenotypes to NSAIDs is shown in [Figure 2](#), while in [Table 3](#), non-steroidal anti-inflammatory drugs causing HSR are classified into particular phenotypes.

Clinical phenotypes of antibiotic hypersensitivity

In the group of 160 patients with hypersensitivity to β -lactams, immediate hypersensitivity (up to 1 hour) was reported only by 15 (9.4%) patients, the occurrence of late

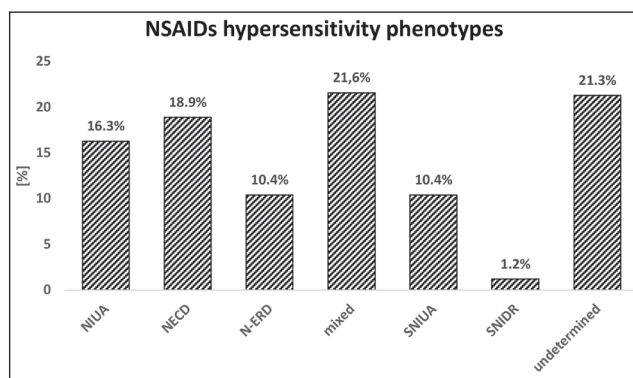


Figure 2 Distribution of NSAID hypersensitivity phenotypes. NSAIDs - non-steroidal anti-inflammatory drugs; NIUA - urticaria or angioedema triggered by NSAIDs; NECD - skin disease exacerbated by NSAIDs; N-ERD - respiratory disease exacerbated by NSAIDs; SNIUA - urticaria, angioedema or anaphylaxis caused by a single NSAID; SNIDR - delayed type reaction induced by a single NSAID

symptoms (1-24 hours after using the drug) by 18 (11.3%), and symptoms that manifested more than 24 hours later by 24 (15%) patients. For the rest of the patients, the time of the reaction was not established. Skin symptoms ($n=72$, 64.3%), followed by respiratory symptoms ($n=14$, 8.8%) and gastrointestinal manifestation ($n=13$, 8.1%) was observed predominantly in people reporting hypersensitivity symptoms after β L.

In contrast, in a group of 112 patients reporting symptoms of DHR to non- β -lactam antibiotics, immediate reaction occurred in 8 patients (7.1%), late in 22 patients (19.6%) and delayed in 29 (25.9%) patients. In this group, the skin symptoms ($n=72$, 64.3%) were most commonly reported, followed by respiratory symptoms ($n=21$, 18.8%).

When comparing the subjects with suspected DHRs to β -lactam and non- β -lactam antibiotics, skin and respiratory symptoms were more commonly reported by patients with suspected HSRs to non- β -lactams, while gastrointestinal symptoms were presented only in those with suspected β L allergy ([Figure 3A](#)). In the group with DHRs related to β L, the onset of symptoms was more often undetermined, while the late reactions (more than 24 hours after drug intake) were more common in patients reporting symptoms to other antibiotics ([Figure 3B](#)). In [Table 4](#), the division of antibiotics that cause hypersensitivity symptoms is presented.

Anaphylactic reactions after medications

General symptoms (in at least two organs) that could be qualified as an anaphylactic reaction were reported by 49 patients, of which nearly half (21; 42.9%) reported a reaction after NSAIDs. The most frequently administered were metamizole (10 patients) and ASA (10 patients), followed by ibuprofen (7 patients). In 11 (22.5%) patients reporting symptoms of anaphylaxis, the probable cause was antibiotics, and in 6 patients (12.2%) other drugs. Ten patients (20.4%), although associated anaphylaxis with the drug, could not provide its name, there was no exact description of the reaction, or several other causative factors were suspected.

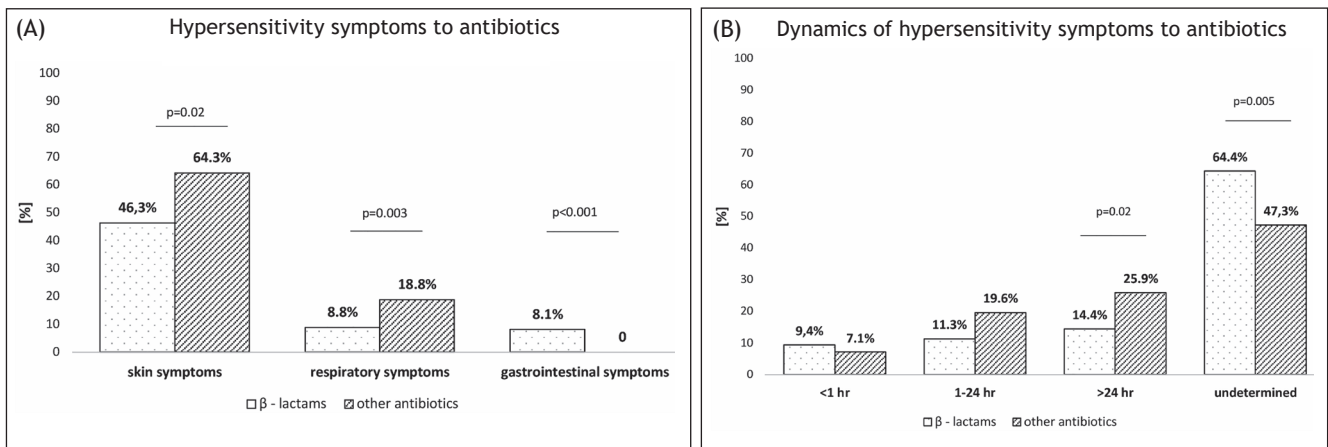


Figure 3 (A) Comparison of symptoms in patients reporting HSR to β-lactams and antibiotics from other groups. (B) Comparison of symptoms dynamics in patients reporting HSR to β-lactams and antibiotics from other groups. Analysis was made with Ch2 test. HSR=hypersensitivity

Table 3 Non-steroidal anti-inflammatory drugs causing HSR classified into particular phenotypes.

Hypersensitivity phenotype to NSAIDs	Name of NSAIDs	n/N (%)
NECD, N=64	aspirin	16/64 (25%)
	ibuprofen	16/64 (25%)
	ketoprofen	12/64 (18.8%)
	metamizole	9/64 (14.1%)
	diclofenac	9/64 (14.1%)
	aspirin	24/55 (43.6%)
NIUA, N=55	ibuprofen	18/55 (32.7%)
	metamizole	15/55 (27.3%)
	ketoprofen	12/55 (21.8%)
	more than 1 NSAIDs	14/55 (25.5%)
N-ERD, N=35	aspirin	18/35 (51.4%)
	ibuprofen	10/35 (28.6%)
	ketoprofen	8/35 (22.9%)
	metamizole	5/35 (14.3%)
SNIUA, N=35	more than 1 NSAIDs	6/35 (17.1%)
	aspirin	14/35 (40%)
	other (ibuprofen - 6, metamizole - 5, ketoprofen - 3, diclofenac - 3, salicylamide - 2, flurbiprofen - 1, meloxicam - 1, benzydamine - 1)	21/35 (60%)
	diclofenac	2/4 (50%)
SNIDR, N=4	other (etofenamat-1, meloxicam - 1)	2/4 (50%)

NSAIDs - non-steroidal anti-inflammatory drugs; NIUA - urticaria or angioedema triggered by NSAIDs; NECD - skin disease exacerbated by NSAIDs; N-ERD - respiratory disease exacerbated by NSAIDs; SNIUA - urticaria, angioedema or anaphylaxis caused by a single NSAID; SNIDR - delayed type reaction induced by a single NSAID

Table 4 Division of antibiotics that cause hypersensitivity symptoms.

Antibiotic group	Amount (n)	Frequency among DHR (n/N=501) [%]
B-lactams	160	31.9%
Macrolides	35	7.0%
Cotrimoxazole	13	2.6%
Clindamycin	13	2.6%
Fluoroquinolones	12	2.4%
Nifuroxazide	5	1.0%
Doxycycline	5	1.0%
Neomycin	5	1.0%
Other	61	12.2%

DHRs - drug hypersensitivity reactions

Diagnosis of drug hypersensitivity

A total of 370 diagnostic procedures were performed in 269 patients with suspected hypersensitivity to the drugs in the years 2009-2019, including 94 oral provocation challenges, 80 skin drug tests, and 196 tolerance tests. Of the oral challenges, 30 (31.9%) were positive, 53 (56.4%) negative, and 11 (11.7%) were doubtful. Skin tests in 8 (10%) cases were positive, 67 (83.8%) negative, and 5 (6.3%) were inconclusive. However, among the tolerance tests with alternative drugs, only 5 (2.6%) gave a result of intolerance (meloxicam - 4, clarithromycin - 1), as many as 172 (87.8%) of its presence, and 19 (9.7%) did not give a definite answer to this question. Among 86 provocations with NSAIDs, 29 (33.7%) were positive, 46 (53.5%) negative, and 11 (12.8%) were doubtful. Aspirin (n = 69) was the most common drug used in the challenge trials in oral, bronchial, and intranasal form. Around 21 (30.4%) tests performed with this drug were positive, 38 (55.1%) negative, and 10 (14.5%) were doubtful. Oral provocation tests with ibuprofen were also carried out (n=9), with 1/3 of them negative and 2/3 positive; 3 trials were carried out with metamizole (2 positive, 1 negative), 1 with ketoprofen which was negative, and 1 with diclofenac which was positive.

Among the tolerance trials with NSAIDs, 141 (87.6%) were negative, 4 (2.5%) positive and, 16 (9.9%) were doubtful (Table 5).

Of the 42 skin prick tests (SPT) performed with antibiotics, 6 (14.3%) were positive, 34 (81%) negative, and 2 (4.8%) were undetermined. Seven provocative trials were

also conducted with antibiotics, in which 1 (14.3%) was positive and 6 (85.7%) negative. Around 35 tolerance trials were also conducted, of which 31 (88.6%) were negative, 1 (2.9%) was positive, and 3 (8.6%) have not been resolved.

In 37 people suspected of being hypersensitive to local anesthetics, SPT and intradermal tests (IDT) were performed, followed by a progressive challenge with a local anesthetic. As a result of the diagnostics performed, only 2 (5.4%) had positive results, 32 (86.5%) negative, and 3 (8.1%) were ambiguous.

Discussion

Among patients who were referred because of suspected hypersensitivity to drugs to a university allergy outpatient clinic, the majority of patients reported symptoms after consuming NSAIDs, followed by antibiotics. Other drugs were found to be less frequent as a cause of hypersensitivity. Studies conducted in other centers seem to confirm the results that non-steroidal anti-inflammatory drugs and β -lactam antibiotics are responsible for over 75% of hypersensitivity reactions to drugs.^{21,22} Antibiotics are the most important cause of pediatric allergy consultation, although non-steroidal anti-inflammatory drugs are gaining importance in adolescents and adults.^{23,24} The incidence of reported drug allergies in the general population of Portugal was 7.8%: 4.5% for penicillin and other β L, 1.9% for aspirin, and other NSAIDs, and 1.5% for other drugs.²⁵

Among the examined patients who were hypersensitive to NSAIDs, aspirin and ibuprofen were the most common symptoms. In 40 people (11.83%) the drug causing the symptoms could not be determined. For comparison, in Portuguese studies, in the group "allergic to NSAIDs", the most commonly administered drugs were: acetylsalicylic acid (18.2%) and ibuprofen (18.2%), followed by nimesulide and meloxicam, and the exact name of the drug causing the reaction was possible to determine in less than 1/3 of cases, more often in the group "allergic to NSAIDs" (59.5%).³⁰ However, it seems that the profile of drugs used may be local and related to the presence on the market and the prevalence of their use. For example, due to the high availability of metamizole in Turkey, in a 2015 study, this drug was the most common cause of hypersensitivity to NSAIDs.²⁶

The current classification of hypersensitivity to non-steroidal anti-inflammatory drugs includes: NECD, N-ERD, NIUA, SINUAA and SNIDR.²⁴ The usefulness of

Table 5 Results of tolerance challenges with NSAIDs.

Drug	Result (n/N [%])		
	Positive	Negative	Doubtful
Meloxicam, N=94	4 (4.4%)	77 (84.6%)	10 (11%)
Celecoxib, N=33	0	31 (93.9%)	2 (6.1%)
Nimesulide, N=25	0	23 (92%)	2 (8%)
Paracetamol, N=11	0	9 (81.8%)	2 (18.2%)
Lornoxicam, N=1	0	1 (100%)	0

NSAIDs - non-steroidal anti-inflammatory drugs

this sub-division was tested in practice in several centers in different countries.^{27,28} In the majority (78.7%) of patients referred due to suspected hypersensitivity to NSAIDs to the Clinic of Immunology and Allergy, based on the documentation, the clinical phenotype could be determined according to the EAACI nomenclature. The most common was the mixed form, then NECD, then NIUA. However, more and more often there are works emphasizing the occurrence mixed forms, i.e., assuming the co-existence of features of at least two phenotypes.²⁹ In a 2015 study conducted in Denmark,³⁰ the co-occurrence of respiratory and skin symptoms was reported in 38% of the patients. In a report published in 2018 by the authors from Spain,³¹ mixed reactions occurring in a total of 261 people in 880 patients with NSAID hypersensitivity related to skin and respiratory tract, concerned more than half (53%) of patients with mixed pattern, skin and digestive system - 99 (38%), skin, respiratory, and digestive system - 16 (6%), and digestive and skin or respiratory system - 8 (3%).

The most common causes of anaphylaxis in epidemiological studies are: drugs, foods, and venom of Hymenoptera insects.³² After excluding pediatric cohorts, drugs are the most common cause of fatal cases of anaphylaxis in reports from the US, UK, Australia, and New Zealand.³³ Among the drugs that were most often cited as the causes of anaphylaxis were: antibiotics, mainly β -lactams, dextrans, contrast agents, allergen extracts, and analgesics, mainly diclofenac.^{32,35} However, the frequency of anaphylaxis caused by individual drug groups is different in different parts of the world. Two of the new studies in France and Portugal reported that antibiotics are still the most common cause of a drug reaction, followed by anesthetics, non-steroidal anti-inflammatory drugs, contrast agents, vaccines, immunotherapy, chemotherapy, and biological drugs.³⁶ In the European Anaphylaxis Registry NORA, drugs with similar frequency as food (in adults up to 65 years of age) and twice as often as food (in people over 65 years of age) were found as the cause of anaphylaxis. Among the drugs causing a systemic reaction, NSAIDs were most frequently indicated, followed by antibiotics.³⁷ Similarly, other series of case reports have identified NSAIDs as the most important cause of drug-induced anaphylaxis, especially in the Latin American population.³⁸ However, a recent Korean study on anaphylaxis during hospitalization has shown that platinum compounds are the main causative agent.³⁹

Verifying the diagnosis based on current guidelines is very important because hypersensitivity reactions may disappear with age, and poor response qualifications can affect the choice of therapy for individual patients which might lead to more expensive and less effective treatments. It is also important to carry out tolerance tests with alternative medicines. Attention should be paid to not recognizing drug hypersensitivity due to lack of reporting,⁴⁰ lack of documentation confirming the occurrence of the reaction, incompleteness of data from the interview, as well as over-diagnose due to abuse of the term "allergy".⁴¹ Most oral provocation challenges (mainly with NSAIDs) and skin tests (mainly with β -lactams and local anesthetics) with drugs suspected of causing

hypersensitivity in patients from Immunology and Allergy Clinic Medical University of Lodz, Poland have not confirmed the diagnosis of drug hypersensitivity. In our material, taking into account the results of skin tests or oral provocation tests with the drug, only 1/5 of the patients confirmed the diagnosis of hypersensitivity, which indicates that it is important to carry out the diagnostic process until the end. Similar data are presented in other publications.

The paper on classification and epidemiology of drug hypersensitivity⁴² cited the results of a 5-year study of 2,150 patients who consulted for drug hypersensitivity (antibiotics, NSAIDs, local anesthetics, anesthetics, vaccines and others, e.g. streptogramin, dihydroergotamine, insulin, and antiretroviral drugs), which showed that after a thorough diagnostics, only 19.3% had a confirmed hypersensitivity reaction to drugs. On the other hand, in a study conducted in Spain in 2005 in 732 patients, drug allergy was suspected, while the diagnosis was confirmed only in 26.6% of cases.⁴³ A similar example is the low percentage (<5%) of confirmed allergy to β -lactams in patients with the "label" hypersensitivity to these antibiotics.⁴⁴

Tolerance challenges with NSAIDs with weak COX-1 or COX-2 selective activity were negative in the majority (87.6%) of patients. Similarly, in most patients with suspected hypersensitivity to β -lactams, an alternative antibiotic was identified (91.2% of the tested patients tolerated non- β -lactam antibiotic). The data from the studies of patients with confirmed hypersensitivity to NSAIDs indicate that weak COX-1 inhibitors such as meloxicam or nimesulide are tolerated by 80-90% of the patients.⁴³⁻⁴⁹ A recent systematic review in N-ERD patients showed that out of 753 coxib tolerance challenges performed by placebo-controlled trial, only 1 was positive, indicating an excellent safety profile of coxibs in these patients.⁵⁰

The present study has its limitations such as qualification only on the basis of initial diagnosis, analysis of only part of the database, and the lack of complete information about the picture of hypersensitivity in the documentation. In addition, the patients were led by 10 different allergists from the clinic, which resulted in discrepancies in the accuracy of descriptions, as well as different approaches to the diagnosis of drug hypersensitivity. The described diagnostic procedures were carried out in expanded group of patients, of which only a part corresponded to the group of patients from the first stage.

Conclusions

It was found that among patients reporting to an allergy outpatient clinic due to drug hypersensitivity, DHRs to NSAIDs are predominant. Less frequently, the patients report reactions after administration of antibiotics, mainly to β -lactams. However, diagnostic tests performed on complaints due to drug-related HRS have ruled out the possibility of hypersensitivity in most of them. The study has also shown that the current classification for NSAIDs hypersensitivity may not include all possible phenotypes of the disease.

Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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