EPIDEMIOLOGY OF SELF-REPORTED DRUG-INDUCED IMMEDIATE-TYPE HYPERSENSITIVITY REACTIONS IN THE SURGICAL POPULATION: A 5-YEAR SINGLE-CENTER SURVEY IN A ROMANIAN ALLERGO-ANAESTHESIA CENTER

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Abstract

Aim: *Immediate-type hypersensitivity drug reactions are frequently under-reported, epidemiological data being imprecise. The aim of our study was to identify the drugs involved and to describe the clinical characteristics of previous immediate-type hypersensitivity reactions in a large series of Romanian surgical patients, and to establish the concordance between in vivo and in vitro tests.*

Methods: *Of the 807 surgical patients referred to our outpatient department of allergo-anaesthesia, we retrospectively enrolled 632 patients with previous drug-induced hypersensitivity reactions. The allergological work-up included a complete allergological history, allergological skin tests and in vitro tests.*

Results: *The drugs involved were: antibiotics in 68% of our patients (with 83.02% being β-lactams), followed by NSAIDs in 43.28% (50.24% of them being metamizol), general anaesthetics in 9.33%, and local anaesthetics or other drugs, each in 6.32% of the 632 patients. The clinical features reported were urticaria in 63.13%, angioedema in 41.77%, bronchospasm in 15.82%, hypotension in 16.61% and cardiovascular collapse in 21.51% of our patients; 31.80% of the referred patients were confirmed as being positive by at least one diagnostic test. The agreement between in vivo tests and BAT was fair (k=0.35), while between in vivo tests and IgE, the concordance was poor (k=0.12).*

Conclusions: *The data obtained from the patients referred to our clinic without any filters and restrictions indicates the pattern of drug-induced immediate-type hypersensitivity reactions and the most frequently involved drugs in Romania. At the end of the allergological work-up we confirmed 31.80% of our patients as having drug-induced hypesensitivity.*

Keywords: hypersensitivity, drug allergy, basophil activation test

Introduction

Drug-induced immediate-type hypersensitivity reactions comprise objectively reproducible symptoms or signs initiated by exposure to the culprit drug, at a dose tolerated by normal subjects, occurring in the first hour after exposure to the culprit stimulus [1,2]. Drug allergy represents an immunologically mediated drug hypersensitivity reaction [3] and is a common problem seen in outpatient clinics, inpatient wards and emergency departments [4]. Hypersensitivity drug reactions represent up to one-third of adverse drug reactions and comprise immediate-type and non-immediate type hypersensitivity reactions, but are frequently under-reported, epidemiological data being imprecise [5,6].

As for all rare events, specific epidemiologic surveys are advised [7]. Specialist allergy clinics are essential in the provision of information for pharmacovigilance databases [3]. Epidemiological studies vary among different countries due to differences in populations, the exposure to drugs as a result of market use, and geographical differences in

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sensitisation, different inclusion/ exclusion criteria and availability of diagnostic tests. Only the use of standardised allergologic examinations could allow the comparison of epidemiological studies among different countries.

The differences in epidemiological studies start from the establishment of a positive diagnosis and might be explained by the fact that the optimal diagnostic approach has been debated [8]. Clinical practice is heterogenous across the world: skin tests are used in 74% of the allergological centers worldwide, the detection of drug-specific IgE in 67% and basophil activation tests in 54% [4]. In order to establish the diagnosis, in our allergo-anaesthesia center we currently take a complete allergological history, perform *in vivo* skin tests and drug-challenge tests under the direct supervision of anaesthesiologists having full resuscitation possibilities. We also perform laboratory research for the *in vitro* diagnosis of drug hypersensitivity depending on availability.

The aims of our study were: (i) to identify the drugs involved in previous hypersensitivity reactions in a large series of surgical patients; (ii) to describe the clinical characteristics of drug-induced immediate-type hypersensitivity reactions; (iii) to describe the diagnostic methods and to analyse the positive allergological tests results, and (iv) to establish the concordance between *in vivo* and *in vitro* tests.

Patients and methods

The enrollment of the patients was approved by the Research Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca. We investigated the patients who were referred by the attending anesthesiologist to the outpatient allergo-anaesthesia department of the Emergency County Hospital of Cluj. The study was conducted starting from January 1st 2008 until December 31st 2012. The inclusion criterion was the presence of previous drug-induced hypersensitivity reactions in the patient's history. All identified patients were retrospectively included in our analysis. The exclusion criteria were history of steroid medication, treatment with antihistamines and pregnancy.

All patients signed the informed consent form for the performance of allergologic *in vivo* and *in vitro* tests and completed, guided by the allergologist, a structured questionnaire containing the complete allergologic history. Allergological *in vivo* tests were performed according to international recommendations [9,10]. The *in vivo* tests included the skin prick test (SPT), the intradermal test (IDT) and the drug challenge test. Flow cytometric analysis of *in vitro* activated basophils (the basophil activation test, BAT) was performed with Flow2Cast technique (Bühlmann Laboratories, Switzerland) to detect the up-regulation of CD63 marker on the basophils after stimulation with drugs and double staining with two monoclonal antibodies, anti-CCR3-PE (human chemokine receptor labeled with phycoerythrin) and anti-CD63-FITC (or Gp53, a glycoprotein expressed on activated basophils). We detected drug-specific IgE antibodies (IgE) using "sandwich"-type radio-immune assay (RIA) with sepharose as solid phase (Pathologie Cellulaire et Moléculaire en Nutrition, Université „H. Poincare", Nancy, France) and anti-IgEs I^{125}-labelled antibodies (Immunotech, Czech Republic). Patients who presented at least one positive diagnostic test were declared as having drug hypersensitivity.

For the characterisation of the study population, a descriptive analysis was performed. Cohen *kappa* index (k) was used to assess the agreement between the *in vitro* tests versus history and skin tests. *Chi-square test* was used to assess the level of significance for the differences in the positivity rates for patient groups.

Results

Starting from January 1st 2008 until December 31st 2012, a total of 807 patients needing surgical interventions under anaesthesia were referred to the Allergo-anaesthesia Outpatient Department of the Emergency County Hospital Cluj, in order to undergo allergological tests for drugs. Of the initial 807 patients, 175 presented atopy and did not have previous drug reactions and were excluded from the present analysis.

We evaluated 632 patients with a suggestive history of a drug-induced immediate-type hypersensitivity reaction; 454 patients were tested for the culprit drugs as indicated in their history; 178 patients refused to undergo allergological tests for the culprit drugs as the reaction declared in their history was severe.

Clinical characteristics

Of the 632 patients, mean age 42 years (range 3-84 years), 482 female and 149 male patients, 91 were under18 years of age (45 girls and 46 boys). The mean time interval between the clinical reaction and the time when the patients presented to our allergo-anaesthesia department was 1938 days (range 45- 19615 days), which is a mean of approximately 5 years. Of the 632 patients, 145 presented atopy.

Self-reported drugs involved in the clinical reactions

Based on clinical history, 430 patients (68%) indicated an antibiotic as being the culprit drug or one of the culprit drugs, 277 patients 43.82%) indicated a NSAIDs drug, 40 (6.32%) local anaesthetics, 59 (9.33%) general anaesthetics and 40 patients (6.32%) indicated other drugs as being responsible for previous drug-induced immediate-type hypersensitivity reactions.

Clinical conditions according to the patients' report

Of the 632 patients, 399 (63.13%) presented urticaria in their history, 264 (41.77%) angioedema, 100 (15.82%) bronchospasm and wheezing, 105 (16.61%) hypotension and 136 (21.51%) cardiovascular collapse; 233 (36.86%) of the patients presented one symptom, while the others presented a combination of two or more symptoms. The symptoms occurring alone were minor in 176 of the patients (urticaria or angioedma alone) or major (bronchospasm,

hypotension or shock alone) in 67 patients.

In vivo and in vitro tests and their contribution in the positive diagnosis of drug-induced immediate-type hypersensitivity reactions

In our patients, we identified retrospectively 3 patient categories, defined as groups A, B and C as follows:

• **Group A:** 172 patients presented at least one positive allergological test for the culprit drug (either SPT, IDT, drug challenge test, BAT or IgE) and their reaction was confirmed. From these, 125 were single-drug reactors, 42 patients had positive tests for two different culprit drugs and 5 patients were confirmed as being positive for 3 drugs.

• **Group B**: 282 patients had all allergological tests negative for the culprit drugs. 18 of them had at least one positive test for an alternative drug and were confirmed as having drug allergy.

• **Group C:** The 178 patients who were not tested for the culprit drugs were tested in order to find safe alternative medication; 11 of them had positive allergological tests for at least one alternative drug and were declared as having drug allergy.

Thus, after the allergological work-up, 201 (31.80%) patients were confirmed as having drug-induced hypersensitivity and 413 (68.19%) had all allergological tests negative.

We performed a total of 634 sets of allergological tests for culprit drugs, 324 for antibiotics, 77 for anaesthetics, 201 for NSAIDs and 32 for other drugs (Table 1).

From the 324 tests performed for antibiotics, 83.02% were for β-lactams as these are the most frequent culprit drugs for antibiotic-induced immediate-type hypersensitivity reactions. From the 201 of the tests performed for NSAIDs, 50.24% were for metamizol, as this is the most frequent antiinflammatory drug incriminated in immediate-type hypersensitivity reactions in our patients.

Of the 634 sets of tests, there were 91 positive SPT for the culprit drugs,102 IDT and 3 positive drug-challenge tests for the drug incriminated as being responsible for the allergic reaction, thus the allergologists confirmed 196 out of the 634 reactions (30.91%). For the *in vitro* tests, there were 73 positive BAT from the total 173 performed (42.19%) and 67 positive IgE from the 132 total radio-immune assays performed (50.75%).

In some of the patients with negative skin tests we performed *in vitro* tests according to availability and we found 15 positive BAT (from the 74 performed in negative-skin patients) and 34 positive IgE (from the 75 performed in negative-skin patients), thus *in vitro* tests confirmed the diagnosis of an immediate-type hypersensitivity reaction in 49 from the 634 tests.

Cross-reactivity with structurally-related drugs was found for antibiotics in 64 of the 269 patients who had a β-lactam antibiotic as culprit drug (23.79%), for NMBAs in 17 of the 34 patients who had NMBAs as culprit drugs (50%) and for NSAIDs in 15 of the 201 patients who had a NSAIDs as culprit drug.

The concordance between the result of the *in vivo* tests and BAT was 0.35 (95%CI 0.22-0.48) and the concordance between the *in vivo* tests and IgE was 0.12 (95%CI 0.047-0.28), as assessed by using Cohen *kappa* index.

Major reactions were caused by antibiotics (63 out of the 324 tested antibiotics, 19.44%), anaesthetics (47 out of 77, 61.03%), NSAIDs (84 out of 201, 41.79%) and other drugs (13 out of 32, 40.62%).

There were 119 positive tests out of the 271 patients presenting with major clinical reactions (43.91%) and 126 positive tests from the 363 patients with minor clinical reactions (34.71%), the difference between the two groups being statistically different (Chi square test, $p=0.0231<0.05$).

Features particular to children

Ninety-four sets of tests were performed in patients aged less than 18 years. The most frequent culprit drugs involved were antibiotics (64 tests), anaesthetics (6 patients), NSAIDs (21 patients), one patient was tested for

Table 1. Allergologic drug tests for culprit drugs.

	Substance	N	SPT	IDT	CT	Cross - reactivity	BAT*	IgE*
Antibiotics	β-lactams	269	34	47	1	64	33/82	55/103
	Other antibiotics	55	10			1	1/3	0/1
Anaesthetics	NMBAs	55	11	14		17	15/26	7/15
	Hypnotics and analgesics	18	1	9			4/6	2/3
	"Unidentified"	8	0	0				
	Local anaesthetics	17	3		1		2/5	2/4
NSAIDs	Metamizol	101	13	22		11	12/35	
	Other NSAIDs	100	10	2		4	4/10	1/6
Other drugs		32	9	4			2/5	

Legend: N = number of patients; SPT = skin prick test; IDT = intradermal test; CT = challenge test; BAT = basophil activation test; IgE = drug specific antibody; "Unidentified" = immediate-type hypersenstivity reaction occuring during general anaesthesia, where no drug could be incriminated based on history; NMBAs = neuro-muscular blocking agents; NSAIDs = non-steroidal anti-inflammatory drugs; *the ratio represents the number of positive *in vitro* tests (BAT or IgE) divided by the total number of *in vitro* tests performed.

local anaesthetic and another for latex.

Of the 64 tests performed for antibiotics, 10 were confirmed by a positive skin test (4 positive SPT and 6 positive IDT) and 6 by a positive IgE in patients with negative skin tests. For antibiotics, 53 tests were performed for β-lactams. Cross-reactivity was found in 14 patients having a β-lactam as culprit drug.

There were 4 patients with previous intra-anaesthetic anaphylaxis for which the NMBA was suspected as being the culprit drug. Three of these were confirmed by a positive SPT and a positive BAT and two presented positive IgE. Two patients presented cross-reactivity for other NMBAs. Latex was found to be the culprit substance in one patient.

From the 21 tests performed for NSAIDs, only one was confirmed by a positive IDT and another one by a positive BAT for metamizol. There were 4 patients presenting cross-reactivity for diclofenac.

Discussion

Hypersensitivity reactions are responsible for mortality and morbidity that are typically underestimated [5,11]. Epidemiological studies are needed in order to confirm and quantify the incidence of these reactions [7]. There is a paucity of tools that allow a definite diagnosis and most of the available ones still require validation, reasons for the existence of scarce epidemiological data [5].

Though there are international guidelines for the diagnosis and management of drug allergy, practices vary across the different regions of the world due to differences in allergology training, practice setups, funding mechanisms and resource limitations [4].

Usually the diagnosis relies on clinical history, skin tests and to a lesser extent *in vitro* testing [12]. None of the currently available diagnostic methods is perfect. The history is often not reliable because multiple drugs are taken simultaneously, while skin and *in vitro* testing is seldom standardised [12]. Challenge tests are potentially harmful, exposing the patients to the culprit drugs, but represent the only way to exclude hypersensitivity reactions when the history is not suggestive for drug allergy, when the history is suggestive and all the other allergological tests are negative, or to exclude cross-reactivity and find safe alternatives for the allergic patients.

Though imperfect, the performance of diagnostic tests would allow further avoidance of the agents responsible for immediate-type hypersensitivity reactions in those patients and provide safe alternatives for future treatments. The retrospective diagnosis is important to assess the reaction precisely, to identify the drugs responsible and cross-reactivity with other drugs, and to avoid subsequent administration of incriminated drugs or agents [13]. The lack of a proper diagnosis and appropriate allergy assessment could lead to fatal reexposure [7].

The knowledge of the characteristics and frequency of immediate-type hypersensitivity reactions and the testing to establish the positive diagnos is would improve the recognition and the management of the reactions. The most frequent culprit drugs for hypersensitivity reactions are antibiotics, especially β-lactams, NSAIDs and other drugs [4,12,14]. Our study confirms the predominance of antibiotics as causative agents for drug-induced immediate-type hypersensitivity reactions in 68% of our patients (with 83.02% of the incriminated antibiotics being β-lactams), followed by NSAIDs in 43.28% (50.24% of them being metamizol), general anaesthetics in 9.33% and local anaesthetics or other drugs, each of the last two categories in 6.32% of our patients.

The knowledge of the clinical manifestations and triggers are crucial to establish strategies for prevention and treatment [15]. The most common clinical features our patients reported were urticaria in 63.13%, angioedema in 41.77%, bronchospasm in 15.82%, hypotension in 16.61% and cardiovascular collapse in 21.51%. In most previous studies, the main clinical manifestations of severe allergic reactions were cutaneous, followed by respiratory and cardiovascular symptoms [15]. Thus, our study is consistent with previous reports from other countries.

Self-reported allergy to drugs are highly prevalent, but poorly explored and currently a firm diagnosis is established by skin tests and blood tests in less than half of the cases, which might be due to a low number of centers or to low referral by other specialists [7,14]. In our allegro-anaesthesia center we perform extensive clinical allergological tests (skin prick test, intradermal test and drug challenge test) and *in vitro* tests when it is necessary. After the allergological work-up, we identified 31.80% of the referred patients as having drug-induced immediate-type hypersensitivity reactions. From the 632 patients, 68.19% had all allergological tests negative. In a large number of patients no allergy can be proven [5]. This might be explained by the loss of sensitivity in time for different agents or by shortcomings of the currently available diagnostic tests [16,17].

Most previous studies show that women are more often affected than men [3,5,11,12,14]. We also confirmed that women tend to report more frequent drug-induced hypersensitivity reactions than men in adults. Whether this is a result of a more frequent drug consumption or a reflection of genetic predisposition and hormone profile is not well known [12].

Scarce specific data are available concerning drug skin tests in children [16]. Most of the drug allergy clinics do not have dedicated pediatric drug allergy services and the principles of when and how to evaluate children with suspected allergy is not different from adults [4]. Most of our patients were adults, but we also investigated 91 children (14.39% of the total number of patients) who were referred to our clinic. We tested them similarly to adults and we conducted a subgroup analysis for children to identify the specificities of allergic reactions in children. Skin tests are feasible and safe in children and improve their safety [16]. As in adults, the most frequent involved drugs were

antibiotics, NSAIDs and anaesthetics, but there was no difference in the sex ratio in the subgroup we studied.

In each patient's allergological survey we performed first the skin prick tests and the intradermal tests, these being the commonest reference tests to which all *in vitro* tests are compared [2]. IgE-dosing has 42.9-75% sensitivity and 66.7-83.3% specificity, while BAT has approximately 50% sensitivity and specificity above 90% for drugs [10,18]. In our study, the agreement between *in vivo* tests and BAT was fair, while there was poor correlation between *in vivo* tests and IgE. The joint use of *in vivo* and *in vitro* tests might increase the sensitivity of the allergological work-up, as some of the patients are only confirmed by the use of the *in vitro* tests.

The prevalence of self-reported drug allergy in a general population has never been reported in the literature [14]. Because of possible biases, including referral bias, spontaneous reporting systems are considered inappropriate [11]. Thus, we can not report the prevalence of drug-induced hypersensitivity, but the data was obtained from the patients referred to our clinic without any filters and restrictions and indicates the pattern of drug-induced immediate-type hypersensitivity reactions and the most frequently involved drugs. All patients who experienced an adverse reaction suspected to be allergic were included. At the end of the allergological work-up we confirmed 30.81% of our patients as having drug-induced hypersensitivity. This survey might underestimate the real picture, similarly to other previous surveys conducted in other countries [4,12,13]. Our study is a retrospective one, a prospective study could be more precise. Immunoassay and BAT were not performed systematically, due to availability, and due to the fact that some of the patients were lost to follow-up. The patients were referred to our department by the attending anesthesiologists after they reported having previous drug-induced reactions suggestive for immediate-type hypersensitivity, so that reactions to medications other than those used in the perioperative period in hospital settings might have been under-evaluated. Some of our patients did not agree to undergo tests for the culprit drugs, the performance of tests on all patients would allow the improvement of the study's precision. These shortcomings in our study on self-reported drug-induced immediate-type hypersensitivity reactions might at least in part be overcome by the large number of patients we studied.

Conclusions

The drugs involved in immediate-type hypersensitivity reactions in a large series of patients in a Romanian allergoanaesthesia center were: antibiotics in 68% of our patiens (with 83.02% being β-lactams), followed by NSAIDs in 43.28% (50.24% of them being metamizol), general anaesthetics in 9.33% and local anaesthetics or other drugs, each of the last two categories being incriminated in 6.32% of the 632 patients. The most common clinical features reported by our patients were urticaria in 63.13%, angioedema in 41.77%, bronchospasm in 15.82%, hypotension in 16.61% and cardiovascular colapse in 21.51%. 31.80% of the referred patients were confirmed as being positive by at least on *in vivo* or *in vitro* test. The agreement between *in vivo* tests and BAT was fair (k=0.35), while between *in vivo* tests and IgE, the concordance was poor (k=0.12).

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