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Research Article

Epidemiology of anaesthetic drug-induced immediate-type hypersensitivity reactions in Romania. A ten-year analysis

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Abstract. Objective: The objectives of this study was to characterize perianesthetic drug reactions encountered in patients presenting to the single Romanian Allergo-Anaesthesia Center from 2008 until 2018. Material and methods: We have tested all patients presenting to the unit and describing symptoms suggestive of immediate type hypersensitivity reactions during exposure to local, regional or general anesthesia from 2008 until 2018. All consenting patients undergo in vivo tests- skin prick tests and intra-dermal tests followed by in vitro testing, as suggested by the allergologist. Results: We have tested 2247 patients between 2008 and 2018. 209 reported a perioperative immediate-type hypersensitivity reaction. 66.5% of our patients were tested at more than 1 year after the perianesthetic reaction and 33.49% at less than 1 year. We have identified 87 (41.62%) patients with positive skin tests to neuromuscular blocking agents (NMBA) out of 209 patients with positive history of hypersensitivity reactions during anesthesia. 29 (13.87%) of our patients had positive skin tests to opioids (fentanyl, remifentanyl and sufentanyl), 16 (7.65%) patients had positive skin tests to hypnotics and 17 (8.13%) patients presented positive skin tests for antibiotics. Conclusion: This is the first study to address the subject of intra-anesthetic drug-induced immediate-type reactions in the Romanian population which reveals the most frequent drugs triggering intra-anesthetic hypersensitivity reactions.

Key Words: hypersensitivity reactions; anesthesia; skin prick test; intradermal test; basophil activation test

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Introduction

Drug-induced hypersensitivity reactions represent a special concern in anesthesia practice, where patients are simultaneously exposed to large number of drugs using the intravenous route in very short period of time.

Patients presenting an immediate type hypersensitivity reaction during anesthesia undergo mandatory retrospective evaluation to identify the culprit substances and cross-reactive compounds, as well as to identify safe anesthetic techniques for future surgical interventions.

The most frequent substances to trigger intra-anesthetic anaphylaxis were the neuromuscular blocking agents (NMBA's) (Mertes et al 2003, Tacquard et al 2017, Fisher et al 1993, Tamayo et al 1999, Harper et al 2016 NAP 6). Theories of previous exposures to cross-reactive compounds have been the most important possible explanations for drug- specific IgE antibodies synthesis and latent sensitization to NMBA's. Recently, it has been demonstrated that the epidemiology of intra-anesthetic anaphylaxis triggers varies over time and among European countries (Garvey et al 2018).

Regional differences are a strong incentive for repeated epidemiological surveys in different countries (Mertes et al 2016). The changing epidemiology of the culprit drugs, the agents that induce immediate-type reactions, highlight the importance of epidemiological studies. These allow the clinicians to become aware of the substances that most frequent trigger intra-anesthetic anaphylaxis and permit the selection of low-risk anesthetic procedures for high-risk patient categories, especially those with previous intraoperative anaphylaxis.

The objective of the present study, to determine the drug agents that are most frequent responsible for intra-anesthetic anaphylaxis in Romanian patients, and to investigate the diagnostic tools used for identifying the culprit agent and safe alternative agents. We have also compared NMBA's skin tests results for patients with positive history of antibiotic hypersensitivity reactions to controls without previous drug allergies to establish if antibiotic hypersensitivity is a risk factor for positive skin tests to NMBA's.

Material and methods

The performance of drug allergy tests for patients with previous immediate-type hypersensitivity reactions was reputedly approved by the Research Ethics Committee of "Iuliu Hațieganu"

University of Medicine and Pharmacy Cluj-Napoca and of Clinical Emergency County Hospital Cluj-Napoca. This retrospective study was performed in the Outpatient Allergo-Anesthesia Unit of the Clinical Emergency County Hospital Cluj-Napoca.

All patients presenting to the unit and describing symptoms suggestive of immediate type hypersensitivity reactions during exposure to local, regional or general anesthesia from 2008 until 2018 were included. We have also included patients with previous signs and symptoms immediate type hypersensitivity reactions induced by antibiotics and healthy controls without previous drug hypersensitivity. Patients were referred to our unit by the attending anesthesiologist or the patients presented voluntarily for testing.

Inclusion criteria were exposure to anesthetics and the presence of signs and symptoms indicating an immediate type hypersensitivity reaction as following: urticaria, itching, flushing, rhinorrhea; angioedema, nausea, vomiting, diarrhea and severe bronchospasm with cyanosis, severe hypotension requiring catecholamine administration, respiratory or cardiac arrest. All patients were accepted for testing at least 6 weeks after the occurrence of the reaction, as suggested by current guidelines (Brockow et al 2013) and according to our local protocol.

Exclusion criteria consisted in ongoing corticosteroid therapy, antihistamine therapy, tricyclic antidepressant therapy and pregnancy.

After giving their informed consent all patients filled in a complex allergological questionnaire regarding their allergy history, ongoing medical treatment, comorbidities and specific details about the perianesthetic hypersensitivity event.

According to our testing protocol, all consenting patients undergo in vivo tests- skin prick test. If the skin prick tests (SPT) are negative, intradermal test (IDT) are performed. Drug concentrations used for skin testing are in accordance with the international guidelines (Brockow et al 2015, Ebo DG et al 2011, Hagău et al 2010) and the tests are performed in a safe environment with access to full monitoring and a trained anesthetist who monitors the procedures. Patients referred by the anesthetist in charge were tested to the incriminated drugs and also to alternative drugs. We have tested the following drug classes adapted to each patient's history: hypnotics (propofol, midazolam, etomidate, ketamine), opioids, depolarising and non-depolarising neuromuscular blocking agents (succinylcholine, atracurium, rocuronium and when available pancuronium or vecuronium), latex, second or third generation cephalosporin, atropine, neostigmine, morphine, pethidine, and tramadol. Drug challenge tests for anaesthetic drugs are not routinely performed in our unit. *In vivo* tests were followed by *in vitro* testing, as suggested by the allergologist.

For flow cytometry assisted basophil activation tests (BAT), 2 ml of EDTA whole blood was obtained from the patients without using the tourniquet and without taking contact with needles for flowcytometric analysis. FlowCAST technique was used (Bühlmann Laboratories AG, Switzerland), with double staining with monoclonal antibodies to human CD63 labeled with fluorescein isothiocyanate (anti-CD63-FITC) and to human chemokine receptor CCR3 labeled with phycoerythrin (anti-CCR3-PE). We considered a positive basophil activation test when more than 5% basophil were activated after the contact with the allergen and when the stimulation index (SI), defined as the percent of activated basophils after exposure to the culprit drug divided by the activated basophils in the negative control, was equal or higher than 2.

Drug-specific IgE antibodies (IgE) were detected using the inhibition test ("sandwich"-type RIA with sepharose as solid phase) (Pathologie Cellulaire et Moléculaire en Nutrition, Université «H. Poincaré», Nancy, France) and anti-IgE I125-labelled antibodies (Immunotech, Czech Republic). We determined radioactivity with the use of LKB gamma-counter (CliniGamma 1272-003, Wallac Oy, Finland). An inhibition index (I) > 20 was considered positive (Hagau et al 201). This test was used in the first two years of the studied period, afterwards we have quit using drug specific IgE antibodies identification in the diagnostic management of perioperative hypersensitivity reaction.

Results

A total number of 2247 patients were tested in our Allergo-Anesthesia Outpatient Department from 2008 until 2018. From these patients, 209 reported a perioperative immediate-type hypersensitivity reaction, the others being tested for antibiotics, minor analgesics or other drugs.

From 209 patients who reported a hypersensitivity reaction during exposure to anesthetic drugs, 79% were women. Mean age of our patients was 45.75 years, with a maximum age of 84 and a minimum age of 3.

Of the 209 patients with positive history of allergic reaction during anesthesia, 42 patients (20.09%) presented atopy. Half of the atopic patients presented at least one positive skin test for the tested drug.

About 73.23 % of our patients presented severe cardiovascular and respiratory symptoms in conjunction with mild cutaneous symptoms.

Concerning the timing of the testing, 66.5% of our patients were tested at more than 1 year after the perianesthetic reaction and 33.49% at less than 1 year.

From 209 patients with a perioperative anaphylaxis history, tested with in vivo and in vitro tests, 48.8% presented negative results in all type of tests.

Three patients out of 209 with positive history of perioperative hypersensivity reaction presented negative skin tests to the tested drugs and positive results in in vitro testing. All these patients were tested less than a year after the perianesthetic reaction, were female patients and one of them presented diamine oxidase deficit and atopy.

We have identified 87 (41.62%) patients with positive skin tests to neuromuscular blocking agents (NMBA) out of 209 patients with positive history of hypersensitivity reactions during anesthesia. 29 (13.87%) of our patients had positive skin tests to opioids (fentanyl, remifentanyl and sufentanyl), 16 (7.65%) patients had positive skin tests to hypnotics and 17 (8.13%) patients presented positive skin tests for antibiotics.

From the 87 patients with positive skin tests to neuromuscular blocking agents, 11 patients had positive skin tests to more than one neuromuscular blocking agent. Only one patient presented positive skin tests for all NMBA tested (atracurium, rocuronium, succinilcholine and pancuronium) and 10 patients had positive tests to at least two NMBA. 15 patients with NMBA positive skin tests presented also positive skin tests to opioids and 2 patients presented positive skin tests to both NMBA and hypnotics.

Table1. BAT results for an aesthetics positive skin tests patients

Causal Agent	+ SPT (n)	+ BAT/ BAT performed (n)	+IgE/IgE performed (n)	+ IDT (n)	+ BAT/ BAT performed (n)	+IgE/IgE performed (n)
Atracurium	6	4/6	2/2	36	6/19	2/5
Rocuronium	10	3/7	2/2	13	1/9	2/2
Succinilcholine	4	1/4	-/4	2	-/2	-
Pancuronium	1	1/1	1/1	1	-/1	1/1
Vecuronium	-	-	-	1	-/1	-
Propofol	-	-	-	4	2/4	-/2
Etomidate	-	-	-	1	-/1	-/1
Midazolam	-	-	-	10	4/6	4/5
Fentanyl	2	-/2	1/2	10	-/5	1/1
Remifentanyl	-	-	-	2	-/2	-/2

SPT- skin prick test, IDT- intradermal test, n- number of patients, + = positive test; BAT- basophil activation test

Table 2. Skin tests results for NMBA's in patients with immediate type hypersensitivity reactions and controls.

	Atracurium		Rocuronium		Pancuronium		Suxamethonium	
	SPT(n)	IDT(n)	SPT(n)	IDT(n)	SPT(n)	IDT(n)	SPT(n)	IDT(n)
Patients	5/98	34/93	2/98	14/97	1/98	7/97	2/98	1/96
Controls	0/72	16/72	0/72	6/72	0/72	1/72	0/72	0/72

SPT- skin prick test, IDT- intradermal test, n- number of patients

In vitro tests results for patients with positive skin tests for specific anesthetic drugs are presented in Table1.

Antibiotics presented positive skin tests results in 17 patients as following: 12 patients presented positive skin tests to beta-lactam antibiotic- 2 patients were positive for penicillin, 2 patients for ampicillin, 4 patients for amoxicillin and 4 patients for second and third generation cephalosporine; 1 patient presented positive skin tests results for carbapenems, 4 patients for quinolones and 2 patients for aminoglycosides. Regarding specific IgE results they were positive for all patients with skin test positivity for beta-lactams and negative for the other antibiotics and negative for the other antibiotic classes. Basophil activation tests were not performed for this category of patients. Seven patients out of the 17 patients with positive results to antibiotic skin testing also presented positive results to specific anesthetic drugs as: 1 patient had positive skin tests to both beta-lactams antibiotics and opioids, 4 patients had positive skin tests to beta-lactams antibiotics and NMBAs, and 1 patient was positive for fluoroquinolone and NMBA skin tests.

Latex was tested using skin prick test and we identified 5 patients out of 209 who presented positive SPT to latex.

We have also included in our study 98 patients with positive history of antibiotic induced immediate type hypersensitivity reactions and 72 healthy controls. Antibiotics responsible for inducing positive skin tests in the patient group were beta-lactams antibiotics in 88 patients (penicillin in 37 patients, ampicillin in 18, amoxicillin in 13, oxacillin in 1, piperacillin in 1 and cefaclor 1, ceftriaxone 1 and cefuroxime 3 patients). 14 patients presented positive skin tests in 2 or more peniciline agents. Trimetroprim-sulphametoxazole induced positive skin tests in 1 patient, quinolones in 6 patients, metronidazole in one and erythromycin in one patient. Skin tests results for NMBA's in the patients with positive history of anaphylaxis induced by antibiotics and the control group are presented in Table 2. 392 skin tests were performed in the patient group and 288 in the control group. We have identified 9 positive SPT and 56 positive IDT in the patient group and 23 positive IDT with 0 positive SPT in the control group.

Discussion

Severe, life-threatening events can occur during anesthesia by drug immediate-type hypersensitivity reactions. Drug- hypersensitivity reactions can result in death or lifelong sequel (Mayorga et al 2019).

Establishing the definitive diagnosis of drug induced anaphylaxis in the perioperative setting is difficult and challenging.

The incidence of hypersensitivity reactions during anesthesia varies with country and with procedures and ranges from 1/1250 to 1/18600 (Mertes et al 2016). In France the estimated incidence is 100.6/ 1 million of procedures with a female predominance (Mertes et al 2016). In our study we also observed a female predominance concerning allergic reactions during anesthesia. We could not estimate the overall incidence of intraoperative anaphylaxis in the Romanian population, as our cohort included only some patients who were referred by the anesthesiologist or who came by themselves for testing. This number of cases might be a gross underestimation of the real number of perioperative immediate-type hypersensitivity reactions.

Substances responsible for immediate allergic reactions during anesthesia recognized by French literature are neuromuscular blocking agents in over 60% of the cases, antibiotics, hypnotics, opioids and other substances. French studies persistently report NMBAs as the first cause for intraoperative anaphylaxis (Laxenaire et al 1999, Dong et al 2012, Mertes et al 2003, Tacquard et al 2017). Latex was responsible for 5.2% of the reactions, an incidence that decreased over time especially with decreasing the use of latex-containing products. Dyes follows

neuromuscular blocking agents and antibiotics with an incidence of 5.4% (Tacquard et al 2017). Close to the French epidemiology, our study revealed NMBA as the most frequent substances responsible for positive skin tests, followed by opioids, antibiotics and hypnotics. Positive skin tests to latex were present in 2.39% which highlights decreasing incidence in latex hypersensitivity due to reduce use of latex compounds. Exposure to cross-compounds that exist in dyes, hairdressing substances and cosmetics might be responsible for latent sensitization for quaternary ammonium compound also found in the structure of most neuromuscular blocking agents. Also, concerns about the local histamine-releasing properties of some of the NMBAs deserve attention, especially for atracurium, which might induce false positive skin tests results. Adherence to skin testing guidelines and procedures is mandatory to avoid false positive results.

Similar reports on United Kingdom, Australian, Flemish, Spanish, and Norway populations highlighted that NMBAs are the main triggers of intraoperative anaphylaxis (Chong et al 2008, Harboe et al 2005, Tamayo et al 1999, Fisher et al 1993]. However, lately, causative agents questioned as being the same among countries. Reactions to antibiotics and hidden allergens have increased (Garvey et al 2018). According to UK NAP6 project, antibiotics are nowadays the commonly identified culprit drugs in the UK (Harper et al 2016 NAP 6). Substantial geographical variability regarding the different drugs or substances involved is reported (Mertes et al 2016).

For investigation of a perioperative hypersensitivity reaction, the allergist in charge should work in close collaboration with the anesthesiologist in order to correctly diagnose the mechanism of the event, to identify the culprit agents, to search for cross-reactivity in the case of neuromuscular blocking agents (NMBA) or antibiotics, with the aim of finding safe alternative anesthesia techniques (Tacquard et al 2016). The investigation of a perianesthetic reaction starts with a complete history of the reaction, preferably obtained from the anesthetist in charge. The anesthesiologist in charge is the most important witness of the reaction and should record all the symptoms of the reaction, all the drugs administered and should take blood samples for tryptase dosing in order to document the immediate type hypersensitivity reaction. The patient should be informed about the severity of the reaction and should become aware about the importance of the future investigation of the event and the importance of finding safe alternatives for the next procedures (Tacquard et al 2016).

After immediate-type hypersensitivity reactions, mast cell mediator secretion can be analyzed. Histamine is the first mediator to be released during an acute allergic event. Tryptase is also an early mediator to be released during hypersensitivity episodes and its values obtained at the time of the event should be compared with the baseline (Montanez et al 2017). No patient in our study had serum tryptase or histamine measurements, as this measurement has not been widespread implemented in local protocols to investigate such reactions. Moreover, tryptase dosing is only available in private laboratories in Romania.

The detailed history is followed by skin tests (prick skin test and intradermal test), and occasionally drug challenge tests. These in vivo tests should be performed as soon as possible to avoid losing test's sensitivity over time but no sooner than 6 weeks after the reaction in order to rule out any potential false-negative reactions (Montanez et al 2017). In our epidemiological study, more than a half of our patients presented for testing at more than 1 year after the perioperative reaction.

Skin tests could identify IgE mediated reactions and for some drug classes they are considered the gold standard for the diagnosis of the hypersensitivity reactions. They should be performed by a trained allergist in a safe environment (Tacquard et al 2016). 67.94% of our positive history patients presented positive skin tests for at least one drug tested.

Retrospective in vitro diagnosis comprises the identification of specific IgE antibodies and the basophil activation test (BAT), which quantifies specific markers from the cell membrane during the activation of the basophils after the antigen contact. Cellular tests and IgE assays avoid patients' exposure to the culprit agent and can improve allergological diagnostic when clinical history and skin tests are redundant. Specific IgE measurements and cellular tests may be useful when the results of the investigations are in discordance (Tacquard et al 2016).. Also, in vitro tests complement skin tests in patients with negative skin tests and also in severe reactions in which in vivo tests are contraindicated (Mayorga et al 2018). In our patients, BAT performance and IgE dosing have been restricted to several research projects. They are not available through the national health programs. As such, we could not test all patients with in vitro assays. None of the available in vivo and in vitro tests has 100% sensitivity and specificity. Due to limitations of the current diagnostic tests, both under and over diagnosis is possible in some of our patients.

Regarding the prediction of positive skin tests for NMBA's in immediate type hypersensitivity induced by antibiotics we have observed that patient group had a higher risk for NMBA's skin test positivity. We also have observed that healthy controls presented positive skin tests to NMBA's which can be explained by cross-sensitivity due to previous quaternary ammonium environmental exposure. Atracurium presented the highest number of positive skin tests in both control and patient group. This might be explained by its ability to induce direct local histamine release when skin tests are performed (Hagau et al 2016).

The limitations of our study are that not all patients suffering intra-anesthetic anaphylaxis have been tested in our unit, so that identified culprits in our cohort might not reflect the true incidences in the entire population with anesthetic drugs allergy. Also, we did not have tryptase measurements as confirmatory laboratory analysis in our cohort. Thus, some of the reactions might not have represented "true allergy". In our patients, some of the reactions have been investigated several years after the suspected allergic event, so that the immune responses may have been damped. Patients with negative retrospective diagnostic tests years after the intraoperative anaphylaxis still have some chances to have had experienced such a reaction. Only few in vitro tests are available for the retrospective investigations of drug anaphylaxis (Mayorga et al 2018).

Conclusion

This is the first study to address the subject of intra-anesthetic drug-induced immediate-type reactions in the Romanian population.

The importance of such epidemiological studies needs to be highlighted: they confer a global image regarding the most frequent

drugs that trigger severe and potential life-threatening reactions in a specific population. They help the clinician choosing the safest anaesthetic technique for at risk patients.
Accurate diagnostic tests and procedural algorithms that take into account the limitations of currently available tests are required.

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