

STUDII CLINICE

Perianaesthetic anaphylaxis. Initial results of the first Romanian allergo-anaesthesia center

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Abstract

Background. There are differences between the results of studies performed in different centres, regarding the substances responsible for anaesthetic related anaphylaxis, although the NMBAs were identified as the most common agents.

Methods. For 2½ years (January, 2008-June, 2010) the patients presenting with perianaesthetic anaphylaxis were analyzed in the Anaesthetic Allergy Centre within the Cluj University. The diagnosis was based on case history, skin prick and intradermal tests, specific IgE measurement and was enforced by BAT. Reactions were defined as IgE-mediated (anaphylactic-type), if positive skin tests, and/or specific IgEs occur.

Results. 22 patients, 13 females, 9 males, ages ranging between 4 and 67 were studied. An IgE mediated mechanism was confirmed in 18/22 patients (82%). The etiological agents were the NMBAs in 9 cases (50%), hypnotics in 3 cases (17%), latex and antibiotics, 2 cases each (11%), and one case each for lidocaine and neostigmine (6%).

Conclusions. In the majority of the cases an IgE mediated mechanism was identified. The most frequent substances responsible for allergic reactions were the NMBAs, followed by hypnotics, latex, antibiotics and other substances, as it resulted from skin tests, and specific IgE measurements.

Keywords: anaesthesia, anaphylaxis, hypersensitivity, perianaesthetic reactions

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Introduction, objectives

Anaphylactic reactions during anaesthesia are rare events. Although the incidence of these hypersensitivity reactions is difficult to ascertain due to uncertainties over the completeness of the data, it is estimated to occur between 1 in 5000 and 1 in 20 000 procedures [1]. An increase above the estimated incidence is noted if a systematically follow-up of adverse reactions during anaesthesia is performed [2]. The determination of the agent(s) responsible for the reaction, the cross-reacting compounds and the identification of the safe

alternatives leads to avoidance of the incriminated substances in sensitized patients, reducing the risk of anaphylaxis during anaesthesia [3, 4]. The aim of our study is to present the initial results of the first Romanian Anaesthetic Allergy Centre (University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca). The diagnostic algorithm and working methodology [5] are based on recommendations in the literature [2, 4, 6-9].

Methods

We carried out a 2½ year prospective single center study between January 2008 and June 2010. We analyzed all patients from the Cluj county area and adjacent counties (the north-western Romania) and isolated cases from other parts of the country that presented themselves to our setting. They described

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the clinical features of an immediate-type hypersensitivity reaction during the perianaesthetic period. Out of 45 referred patients, 22 consented to complete all in vivo and in vitro investigations needed for identifying the causative agents of the allergic reaction. The case histories were completed by interviewing the patient and by documentation offered by the referring anaesthetist or physician. We collected data on age, sex, general and atopic history, previous anaesthesia, anaesthetic drugs given before the anaphylactic-type reaction, time interval between administration of the drugs and the onset of the reaction, and the time interval between the clinical reaction and the moment of presentation.

The severity of the reactions was classified according to a standard approach, based on clinical features. The mild or grade I reactions consisted of cutaneous generalised signs such as erythema, hives, with or without angioedema. Moderate multivisceral signs with cutaneo-mucous signs, hypotension, tachy- or bradycardia, bronchial hyperreactivity made evident by cough or dyspnoea corresponded to grade II. Multivisceral severe signs, such as collapse, tachy- or bradycardia, arrhythmia, bronchospasm with or without cutaneous signs, that are life-threatening and impose specific therapy, correspond to grade III, and cardiac arrest to grade IV [10].

The diagnosis was based on history, skin prick and intradermal tests, total and specific IgE determinations [2]. As a new approach we added to the allergological work-up the basophil activation test to enforce our results [11, 12] For BAT and for specific IgE measurements the blood sample was taken before skin tests, in the same day. There was no use of H1 and H2 antihistamines, corticosteroids or antidepressants, nor pregnancy or breast-feeding among the patients in the moment of testing.

The prick (SPT) and intradermal skin tests (IDT) were performed using commercially available solutions of anaesthetic agents and other drugs used in the perianaesthetic period. Previously, we had obtained the approval of Research Ethics Committee of our university hospital and the patients' informed consent. Normal saline solution (0.9% NaCl) was used to dilute these commercial substances. For latex we used the commercial solution for SPT from Stallergenes (Antony, France).

The tested substances were neuromuscular blocking agents atracurium-Tracrium GSK, pancuronium-Pavulon, Organon, rocuronium-Esmeron, Organon, suxamethonium-Lysthenon, Nycomed, vecuronium-Norcuron, Organon), hypnotics (propofol-Propofol Lipuro, B Braun, etomidate-Etomidat Lipuro, B Braun, thiopental-Thiopental sodium, Eipico and midazolam-Midazolam Torrex), opioids (meperidine-Mialgin,

Zentiva, fentanyl-Fentanyl Torrex and remifentanyl-Ultiva, GSK), local anaesthetics (bupivacaine-Marcaine, Astra-Zeneca, lidocaine-Xilina, Zentiva), antibiotics, latex, colloids (Gelofusine, B Braun), disinfectants (povidone iodine, CVS Pharmacy) and other (neostigmin-Miostin, Zentiva, atropine-Atropina, Zentiva, metamizol-Algocalmin, Zentiva) substances. We investigated all suspected substances and all potential incriminated drug classes in order to identify the cause of anaphylaxis, and also in order to recommend a range of agents likely to be safe for future use [2]. The concentrations used for the SPT and the IDT are those recommended by current guidelines [4, 6], and are presented in Table 1.

Table 1. Maximal concentrations for skin tests (prick and intradermal tests)

Substance	Skin test Concentration	
	SPT (mg/ml)	IDT (µg/ml)
Atracurium	1	10
Rocuronium	10	100
Suxamethonium	10	100
Pancuronium	2	200
Vecuronium	4	400
Midazolam	1	250
Propofol	10	1000
Fentanyl	0.05	5
Remifentanyl	0.05	5
Lidocaine	10	1000
Neostigminium	0.5	5
Cefoperazone	2	2000
Ceftriaxone	2	2000

SPT – skin prick test; IDT – intradermal test; maximal concentration for skin test – the concentration that once exceeded produces nonspecific or irritative skin reaction, leading to false positive results (concentrations recommended by SFAR [4] except for midazolam [19])

The prick and intradermal tests were performed in accordance with international Recommendations [4, 6] and according to the testing methodology described by authors with experience in skin testing [13]. We used 1% histamine as positive control (Histamine 1%, Stallergenes) and NaCl 0.9% as negative control. The prick test was regarded as positive when the wheal diameter was 3 mm larger than the negative control, within 20 minutes. In the intradermal test the injecting wheal area (3-4 mm diameter) was marked initially and 20 minutes after testing. An increase in diameter greater than 3 mm or the doubling of the initial injection wheal represented a positive result [4, 14]. In the case of NMBAs, all the substances in current use in our setting were tested for identifying the cross-reactivity [3, 4, 6].

Flow cytometric analysis of basophils activated in vitro was performed with Flow2Cast technique (Bühlmann Laboratories, Switzerland), measuring the up-regulation of CD63 (activation marker on the basophils). The result was considered positive after challenge with a specific drug allergen, when the percentage of activated basophils was = 5% over the spontaneous activation observed for the negative control. Also, in case of positivity, the stimulation index calculated as the ratio between the percentage of activated basophils and the negative control was = 2 [12, 15].

We measured *drug-specific IgE antibodies (IgEs)* using a “sandwich”-type radio-immunoassay (RIA) with sepharose as solid phase (Pathologie Cellulaire et Moléculaire en Nutrition, Université „H. Poincaré”, Nancy, France). For neuromuscular blocking agents (NMBAs), meperidine and midazolam, we used quaternary ammonium-sepharose (QAS) as allergen for the first stage (A = detected radioactivity in the first stage). If the QAS antibodies were present, we performed an inhibition test with specific drugs in the second stage (B = detected radioactivity in the second stage). Inhibition (I) was estimated from the radioactivity adsorbed to the sepharose in the first and the second stages as $I = A - B / A * 100$. The test was positive when the specific IgE binding radioactivity was modified with more than 20%. We were not able to perform specific IgE detection, for antibiotics and neostigminum, due to technical difficulties.

We defined the pathogenic mechanism of the reactions in accordance to the nomenclature proposed by the EAACI and WAO [16] into IgE-mediated and non-IgE mediated reactions, depending on the results of skin prick tests, intradermal tests and specific IgE determination. Mertes and the GERAP members [10] included the IgE-mediated reactions in the ‘anaphylactic’ group (positive skin tests and/or positive specific IgE) and the non-IgE-mediated in the ‘anaphylactoid’ group (negative skin tests and negative specific IgE). This terminology is still in use [2, 10]. The features of anaphylactic and anaphylactoid reactions are clinically indistinguishable [2].

The statistical analysis was performed using Excel software (2003, Microsoft Corporation, Seattle, USA). Comparisons were done using CHI Square Test, with a statistical significance of $p < 0.05$. We used the Yates correction for small groups.

Results

22 subjects (an average of 9 patients/ year, 13 females (59%) and 9 males (41%), aged between 4 and 67 years (35 ± 19 years) with perianaesthetic immediate type hypersensitivity reactions were included in

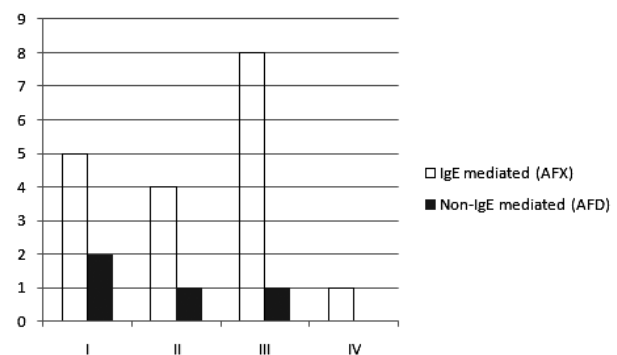
the current research. The sex, age group, previous history of uneventful general anaesthesia, self reported drug allergy, the time interval between the anaesthetic anaphylactic-type reaction and the allergy testing are presented in Table 2.

We obtained *positive skin tests* in 18 patients, 2 for latex and 16 for drugs. Nine patients (50%) reacted to NMBAs, 2 patients to latex (11%), 2 to antibiotics (cephalosporins 11%), 2 to midazolam (11%) and one (6%) for each of the following: propofol, lidocaine and neostigminum. The IgE mediated mechanism (anaphylactic group) was confirmed in 18/22 (82%) of the reactions, and the non IgE mediated mechanism (anaphylactoid group) in 4/22 (18%) (Table 2).

In 12 of the 16 drug allergy cases (75%) the positive skin test results were correlated with positive basophil activation test. In 11 cases of 13, where IgEs was performed, the positive skin test results were correlated with the positive specific IgE (85%). For NMBAs, the positive skin tests were correlated in 89% with positive specific IgEs and in 78% with positive basophil activation tests.

A positive result to more than one NMBA (*crossreactivity*) was observed in 56% of patients with positive prick and intradermal tests, in 42% with positive BAT and in 63% with positive specific IgEs.

We observed mild reactions (grade I) in 7 patients (32%), grade II reactions in 5 patients (23%), grade III in 9 patients (41%), and in one case (5%) grade IV reaction. The anaphylactoid reactions represented 29% in the group of mild reactions, and only 13% in the group of moderate-severe reactions. The distribution of the anaphylactic and anaphylactoid reactions by clinical severity grades and by sex are presented in Figure 1, respective Figure 2.



AFX – anaphylactic reaction, IgE mediated; AFD – anaphylactoid reaction, non-IgE mediated; I – cutaneous generalised signs: erythema, hives, with or without angioedema; II – moderate multivisceral signs with cutaneo-mucous signs, hypotension, tachycardia, bronchial hyperreactivity (cough, dyspnoea); III – multivisceral severe signs, life-threatening and imposing specific therapy: collapse, tachy- or bradycardia, arrhythmia, bronchospasm, the cutaneous signs could appear only after blood pressure normalization; IV – cardiac arrest [10]

Figure 1. Distribution by severity grades of anaphylactic and anaphylactoid reactions

Table 2. Synthesis on patient demographic data, history and positive in vivo and in vitro diagnostic tests allowing the identification of the ethiologic agents involved in perianaesthetic reactions

P A T I E N T D A T A							IN VIVO and IN VITRO POSITIVE TESTS				E T H I O L O G Y	
Nr.	Sex	Age group	Δt	SRDA	PUGA	Severity grade	Positive SPT	Positive IDT	Positive Flow	Positive IgEs	Main	Possibly associated
1	F	51>60	>2Y	AB	no	I					anaphylactoid reaction	
2	F	11>20	0-6M		no	III	latex gentamicine				latex	gentamicine
3	F	21>30	0-6M		yes	II		midazolam	midazolam		midazolam	
4	M	61>70	0-6M		yes	III	rocuronium		rocuronium	rocuronium	rocuronium (NMBA)	
5	F	31>40	>2Y		no	II					anaphylactoid reaction	
6	F	11>20	>2Y	AB	no	I	atracurium rocuronium suxamethonium pancuronium rocuronium		atracurium rocuronium	atracurium rocuronium pancuronium	NMBA	
7	M	11>20	6M-1Y		no	I	suxamethonium fentanyl		rocuronium	rocuronium fentanyl	NMBA	fentanyl
8	M	61>70	0-6M	Other	no	III	cefoperazone		cefoperazone		cefoperazone	
9	M	31>40	>2Y	Other	yes	III		atracurium rocuronium pancuronium		atracurium rocuronium pancuronium	NMBA	
10	F	21>30	0-6M		no	III			suxamethonium		anaphylactoid reaction	
11	M	41>50	0-6M		yes	III		ceftriaxone			ceftriaxone	
12	M	21>30	1Y-2Y		no	I	suxamethonium	atracurium		rocuronium pancuronium	suxamethonium atracurium (NMBA)	
13	F	51>60	>2Y	AI+ Other	yes	I		neostigminum midazolam	neostigminum midazolam	midazolam	neostigminum	midazolam
14	F	31>40	>2Y		no	II	latex				latex	
15	F	31>40	>2Y	AB	yes	IV		atracurium midazolam fentanyl remifentanyl	atracurium rocuronium suxamethonium pancuronium midazolam	atracurium rocuronium pancuronium fentanyl remifentanyl midazolam tiopental	NMBA	midazolam tiopental (hypnotics) fentanyl remifentanyl (opioids)
16	F	21>30	0-6M		yes	II		midazolam	midazolam	midazolam	midazolam	
17	F	61>70	0-6M		yes	III	atracurium rocuronium		atracurium rocuronium pancuronium	atracurium rocuronium pancuronium	NMBA	
18	F	31>40	1Y-2Y	AB	no	I		propofol		propofol	propofol	
19	M	51>60	0-6M	AI	yes	III	lidocaine		lidocaine	lidocaine	lidocaine	
20	M	01>10	0-6M		no	II	suxamethonium		suxamethonium		suxamethonium (NMBA)	
21	F	31>40	>2Y	AB	no	III		vecuronium		vecuronium	vecuronium (NMBA)	
22	M	01>10	0-6M		no	I					anaphylactoid reaction	

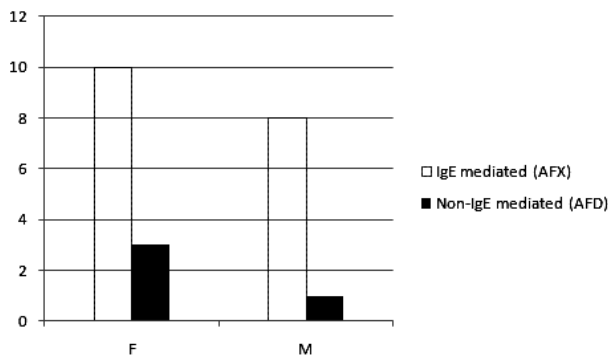
F – female; M – male; Δt – time between the perianaesthetic allergic reaction and the moment of the allergologic survey; M – month; Y – year; SRDA – self reported drug allergy to other than drugs used in the perianaesthetic period; AB – antibiotics; AI – antiinflammatory drugs, including pyrazolones; PUGA – previous uneventful general anaesthesia; SPT – skin prick test; IDT – intradermal test; Flow – flowcytometric basophil activation test, Flow2Cast technique; IgEs – drug allergen specific IgE, RIA technique; I, II, III, IV – severity grade of clinical reactions in a standard approach [10]

The correlation between the type of reaction and sex, severity grade and total IgE value was not statistically significant (Table 3).

Discussion

The incidence of the perianaesthetic anaphylaxis in Romania is currently unknown. The initial results of the first Romanian Allergo-Anaesthesia Center suggest

that the causes and contributing factors are similar to other European countries. We observed a female predominance (59%) of perianesthetic allergic reactions in our patients. This female predominance was also observed in France for both the anaphylactic (67.6%) and the anaphylactoid reactions (69.9%), with an ascending tendency in the last years [10]. In Norway a female to male ratio of 3:1 was observed, according to the study of Harboe et al. [17], and of 3:2 in Spain



F – female; M – male; AFX – anaphylactic reaction, IgE mediated; AFD – anaphylactoid reaction, non-IgE mediated

Figure 2. Female and male distribution of anaphylactic and anaphylactoid reactions

(Lobera et al., [18]). The reason for the female predominance is unknown.

Applying the definition for *anaphylactic (IgE-mediated) and anaphylactoid (non-IgE mediated) reactions* proposed by Mertes et al. [10], we established in our study that 81% of reactions were of anaphylactic type. Other European authors, using the same criteria for defining the reaction type also observed that the anaphylactic reactions were predominant (69% in France [10], 56% in Spain [18], and 71.1% in Norway [17]). Two thirds of our patients developed a moderate-severe clinical reaction, and only one third a mild one. The anaphylactic reactions seem to be more severe than the anaphylactoid reactions in our patients, accordingly to the French results [10].

The methodology of skin testing used in our work [5] was in accordance with the recommendations published in the guidelines [4, 6], described in review articles [3, 7], and based mainly on the French experience [4]. The maximal concentrations for skin prick and intradermal tests were also similar to those recommended in the guidelines or in the specific literature [3, 4, 6-8] except for midazolam, where we applied a lower concentration in intradermal tests (250 µg/ml) to avoid nonspecific positive results [19]. The results of the skin tests are important and bear a higher clinical relevance than the serum antibody tests. This relevance is a result of the fact that specific IgE tests measure in vitro interaction between the drug molecule and the antibody combining site, while skin tests detect drug induced cross-linking of cell bound IgEs via the antibody combining sites, therefore the result is a mediator release [20]. The skin tests were our main diagnostic tool on grounds that provocation tests are not advisable in anaesthetics for ethical reasons. The skin tests are considered to be more sensitive than the in vitro tests [21]. There was a 93% overall agreement

Table 3. Correlation between the reaction type and total IgE level, severity grade and sex

Reaction type		AFX	AFD	p
Total IgE	> 87	9 (50%)	1 (25%)	0.723918*
	≤ 87	9 (50%)	3 (75%)	
Severity grade	mild	5 (27.8%)	2 (50%)	0.787372*
	moderat-severe	13 (72.2%)	2 (50%)	
Sex	F	10 (55.6%)	3 (75%)	0.878153*
	M	8 (44.4%)	1 (25%)	

AFX – anaphylactic reaction, IgE mediated; AFD – anaphylactoid reaction, non-IgE mediated; F – female, M – male; * Yates correction

between SPT and IDT, and by using both tests we improve predictability by 67% [22].

Our results show that *neuromuscular blocking agents* were the leading etiological agents (50%) in the group of patients with anaphylactic reactions. The literature also points out that NMBAs are considered to be the main compounds involved in perioperative anaphylaxis [3, 4]. The report of Mertes and the GERAP members on the anaphylactic and anaphylactoid reactions occurring during anaesthesia [10], a retrospective epidemiologic survey conducted between January 2001 and December 2002, emphasizes that the NMBAs were involved in 55% of the anaphylactic reactions. The NMBAs were the most frequently observed causes of perianaesthetic anaphylaxis in Norway also, in 93% of cases with IgE mediated reactions [17], but not in Spain, where antibiotics were the lead cause [18], or in Denmark where disinfectants played the lead role [23]. NMBA crossreactivity was observed in our work in 56% of patients by skin tests, 63% by IgEs and 42% in BAT. Mertes et al. [10] reported cross reactivity of 63.4% between NMBAs. In the literature, a higher cross reactivity was observed in IgE assays than in skin tests [3], consistent with our observations.

The *hypnotics* come second in our report, unlike the results of one of the epidemiologic French surveys, with hypnotic induced reactions in only a small subset of patients [10]. It is interesting to observe that another epidemiological survey conducted in France between 1984 and 1989 placed the hypnotics in the second position after NMBAs [10]. The allergic reactions to *antibiotics*, representing the third cause of anaphylaxis in our survey and also in France [10] were most frequently observed in Spain, mainly to betalactams [18], and were not observed in Norway [17]. *Latex allergy*, placed on the same position as antibiotics in our work,

was the second cause of anaphylaxis in France and Norway [10, 17], but weakly represented in Spain [18]. We did not observed positive tests to disinfectants even if surprising results came from Denmark, where 5 of 36 patients presented positive skin tests to chlorhexidine [23]. The origin of the differences regarding the substances involved in reactions between countries is hard to explain but may reflect cross reactivity with other drugs commonly used in those countries [20]. For example, in Norway the extensive use of pholcodine in cough mixtures seems to induce latent sensitization to substituted ammonium containing molecules, and could explain the high incidence of reactions to NMBAs in this country [24-26]. In Romania, a similar situation could exist, with dextrometorphan containing cough mixtures.

In patients without previous exposure to anaesthetic drugs sensitization could be induced by other cross reactive antigens.

Differences in reporting patterns between countries also could exist. The fact that only 22 out of 45 of our patients completed all the investigations needed for the allergologic survey is hard to explain, and may be educational reasons or test-related adverse reactions concerns. The preliminary results of the Danish Anaesthesia Allergy Centre also points that only 36 out of 68 referred patients completed the study [23].

36% of Romanian patients, as well as 66.67% of the Spanish and 67.5% of Norwegian patients presented previous uneventful general anaesthesia in their medical history [18, 17]. We observed that 41% of our patients with perianaesthetic anaphylaxis presented self reported drug allergy, mainly to antibiotics and anti-inflammatory drugs. The Norwegian report shows that 25.35% of patients presented history of non-anaesthetic drug adverse reactions [17], comparative to the self reported drug allergy in the general population that is 7.8%-8.3% [27, 28]. The positive tests to anaesthetics in patients with allergy to drugs other than anaesthetics could reflect a latent sensitization with unknown clinical relevance [29, 30].

Taking into account that in perianaesthetic allergy none of the diagnostic test are infallible, because a validation requiring a challenge with anaesthetic drugs is not possible [2] we decided to improve our decision by adding the flow cytometric basophil activation test (Flow2Cast technique) even if is not currently recommended for routine clinical practice. In our work positive skin tests to drugs were correlated with positive basophil activation test in 75% of cases, and with 78% of cases if we select the NMBAs. The basophil activation test resembles to in vivo immunological mechanism leading to symptoms [31] suggesting that this method could have a good clinical relevance, and it is not restricted by an important requirement in antibody

immunoassays, related to drug conjugation with carrier proteins or spacers use. For NMBAs a BAT specificity of 100% and sensitivity of 91.7% were obtained also for betalactams a sensitivity of 50% and a specificity of 93.3% [21]. Relative to specific IgEs measurement, we have chosen a method (SAQ-RIA) with a high sensitivity and specificity (89-97%, respective 97%) for NMBAs that also allow inhibition assays, a method also was used in the French survey [10]. Specific IgEs can be determined only for a limited number of substances. By combining skin tests and in vitro tests we could improve the sensitivity of these methods, as was shown for antiinflammatory drugs, from 56% to 96% [21].

Conclusion

The perianaesthetic allergic reactions were encountered more frequently in female patients. The anaphylactic (IgE mediated) mechanism was identified in most cases, and were associated with more severe clinical features. As a result of the allergological work-up the NMBAs were the main culprit agents, followed by hypnotics, antibiotics, latex and other substances. For all tested patients the allergologic survey also identified safe alternatives for subsequent anaesthesia. An important percent of subjects mentioned self reported drug allergy to other than anaesthetics. Larger epidemiologic surveys on the perianaesthetic anaphylaxis in our country could offer more data on the risk factors, offending compounds and valuable informations on the dynamic changes of the sensitization profiles.

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Reacțiile anafilactice perianestezice. Rezultatele inițiale ale primului centru român de alergoanestezie

Rezumat

Obiectiv. Rezultatele prezentate de către diferite centre nu sunt identice în ceea ce privește agenții implicați în declanșarea reacțiilor alergice perianestezice, deși agenții blocați neuromusculari au fost cel mai frecvent incriminați.

Material și metodă. Studiul cu o durată de 2½ ani, a inclus pacienții care s-au adresat Centrului de Alergoanestezie al UMF Cluj, prezentând reacții de hipersensibilitate de tip imediat în cursul perioadei perianestezice. Diagnosticul etiologic s-a bazat pe istoricul clinic, testele cutanate alergologice și determinarea IgEs la medicamente. Testul de activare a bazofilelor prin citometrie de flux a fost realizat suplimentar pentru susținerea diagnosticului. Reacțiile au fost definite ca fiind IgE mediate (anafilactice), dacă s-au obținut teste cutanate, și/sau IgEs pozitive.

Rezultate. Dintre cele 22 de cazuri (13 femei și 9 bărbați), 18 au prezentat reacții IgE mediate (82%).

În grupul reacțiilor anafilactice, 9 (50%) au fost declanșate de curare, 3 de către hipnotice (17%), 2 la latex (11%), 2 la antibiotice (11%) și câte un caz pentru lidocaină și neostigmină (câte 6%).

Concluzii. Mecanismul IgE mediat a fost identificat în majoritatea cazurilor. Substanțele cele mai frecvent

implicate au fost agenții blocați neuromusculari, urmași de hipnotice, antibiotice, latex și alte substanțe, după cum a rezultat din efectuarea testelor cutanate alergologice și a determinărilor de IgE specifice.

Cuvinte cheie: anestezie, anafilaxie, hipersensibilitate, reacții perianestezice