Is a positive history of non-anaesthetic drug allergy a predictive factor for positive allergy tests to anaesthetics?

Natalia Hagau,¹ Nadia Gherman-Ionica,² Denisa Hagau,³
Sebastian Tranca,¹ Manuela Sfichi⁴ & Dan Longrois⁵

¹Department of Anaesthesia and Intensive Care, University of Medicine and Pharmacy 'Iuliu Hatieganu' Cluj-Napoca, Romania, ²Immunology and Allergology, University of Medicine and Pharmacy 'Iuliu Hatieganu' Cluj-Napoca, Romania, ³Memorial Hospital of Rhode Island, Brown University, Pawtucket, RI, USA, ⁴Department of Immunopathology, Clinical Emergency County Hospital Cluj, Romania and ⁵Assistance Publique-Hôpitaux de Paris (APHP), Department of Anaesthesia and Intensive Care, Bichat-Claude Bernard Hospital and University Paris 7, Paris, France

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- International recommendations stipulate not to perform skin tests to a drug in the absence of a clinical history consistent with drug allergy.
- In 2006, two publications showed that a positive history of non-anaesthetic drug allergy was the only predictive factor for allergy to anaesthetic drugs when the screening was done in a general surgical population.
- They concluded that their data supported the international recommendations that a prick test to neuromuscular blocking agents (NMBAs) is indicated only among those patients who have a history to an adverse reaction to them, but at the same time in the case of 2.8% of the patients with no history of peri-anaesthetic allergy, the NMBA to which they showed a positive prick test was avoided.

WHAT THIS STUDY ADDS

- The novelty of the study is our approach regarding a selected population (volunteers from a general surgical population with a prior history of immediate type hypersensitivity reaction to non-anaesthetic drugs) in which we performed pre-operative skin tests and *in vitro* tests to NMBAs and other anaesthetics.
- Ten per cent of our selected patients had a positive prick test to NMBAs and the results of the basophil activation test (BAT) agreed with prick tests in 83% of patients. BAT is a test that detects IgE mediated effector cell activation, overcoming the concerns related to skin reactivity at different drug concentrations.
- Our results could define a special risk group for intra-anaesthesia anaphylaxis, and they might lead to the necessity of changing the existing pre-operative allergy approach.

Correspondence

Dr Natalia Hagau, Department of Anaesthesia and Intensive Care, Clinical Emergency County Hospital of Cluj, 400006 Clinicilor 3-5, Cluj-Napoca, Romania.

Tel.: +40 264 599 438

Fax: +40 264 599 438

E-mail: hagaunatalia@gmail.com

Keywords

anaesthetic drugs, basophil activation test, drug allergy, NMBA, skin tests, specific IgE

Received

10 June 2011

Accepted

26 September 2011

Accepted Article Published Online

11 October 2011

AIMS

International recommendations stipulate not performing screening skin tests to a drug in the absence of a clinical history consistent with that specific drug allergy. Nevertheless, two publications showed that a positive history of non-anaesthetic drug allergy was the only predictive factor for a positive skin test when screening for allergy to anaesthetic drugs was done. We selected from a surgical population 40 volunteers with a prior history of allergy to non-anaesthetic drugs in order to analyse the prevalence of positive allergy tests to anaesthetics.

METHODS

The selected adult patients were tested for 11 anaesthetic drugs using *in vivo* tests: skin prick (SPT) and intradermal (IDT) tests and *in vitro* tests: the basophil activation test (BAT) and detection of drug-specific immunoglobulin E (IgE).

RESULTS

The prevalence for the positive SPT and IDT was 1.6% and 5.8% respectively. The result of flow cytometry agreed with the SPT in five out of seven positive SPT (71%). IgEs confirmed two positive SPT with corresponding positive BAT. Ten per cent of the patients had a positive prick test to neuromuscular blocking agents (NMBA). For midazolam none of the SPT was positive, but 11 patients had positive IDT nonconfirmed by BAT.

CONCLUSION

The prevalence of positive *in vivo* and *in vitro* allergy tests to NMBAs is higher in our study population. This could be an argument for pre-operative SPT to NMBAs for the surgical population with reported non-anaesthetic drug allergies. A larger prospective study is needed to validate changes in clinical practice.

Introduction

There has been a continuing debate in the scientific community concerning the clinical value of systematic preoperative screening for anaesthetic drug allergy using skin tests in the absence of clinical history. There has been an agreement that skin tests should only be performed for patients with a credible history of peri-anaesthetic hypersensitivity in order to identify the culprit drug [1], but it has been stated that systematic screening for anaesthetic drug allergy, in the absence of credible history, is not recommended [2–4]. This is based on the fact that the low incidence of allergic reactions to anaesthetic drugs in the general population renders screening unreasonable given the limitations of the currently available tests. Screening tests for anaesthetic drug allergy might nevertheless prove valuable when a group of patients with a defined risk profile is selected. In 2006 Tamayo *et al.* found that when screening for allergy to anaesthetic drugs in a surgical population, the only predictive factor for a positive skin prick test (SPT) was a positive history of allergy to non-anaesthetic drugs [1, 5]. In contrast, in 1999 Porri *et al.* found no risk factors (atopy or history of drug allergy) for the positive SPTs when screening for allergy to neuromuscular blocking agents (NMBA) was done in a general population [6].

The progression from a positive SPT to clinical allergy is multifactorial but the presence of a positive test might be proof of latent sensitization, with possible subclinical, minor or major clinical expression [7]. The clinical predictive value of the skin tests cannot be determined as performance of challenge tests to anaesthetic drugs is limited by ethical concerns. Performing additional *in vitro* allergy tests could provide complementary information on the matter. In Norway Florvaag *et al.* found the prevalence of drug-specific IgEs for suxamethonium in a population with risk factors (positive allergy history) was 3.7%, higher than in the group without risk factors, 0.4% (blood donors) [8]. There were no citations in the literature concerning the use of the basophil activation test (BAT) in screening for anaesthetic drug allergies, in patients without prior history of anaesthetic drug allergy.

For the above mentioned reasons, we designed the present prospective study in order to analyse the prevalence of positive *in vivo* and *in vitro* complementary allergy tests (the BAT and IgEs) to anaesthetic agents in a group of surgical patients with history of allergy to non-anaesthetic drugs. The higher prevalence of positive *in vivo* and *in vitro* allergy tests to anaesthetic agents for this group of patients could define a special risk group of intra-anaesthesia anaphylaxis, and it might lead to the necessity of changing the existing preoperative allergy approach.

Methods

After the approval of the Research Ethics Committee of the University Hospital of Cluj-Napoca and after obtaining

patients informed consent, a total of 40 consenting adult volunteers with previous drug allergies to non-anaesthetic drugs were prospectively included. The inclusion criterion was history suggestive of an immediate-type hypersensitivity reaction caused by antibiotics or anti-inflammatory drugs. In the subset of anti-inflammatory drugs, metamizol was the culprit agent and it is known that it produces IgE-mediated reactions [9]. This inclusion criterion is essential in the selection of diagnostic tests that correspond to the underlying mechanism. Immediate type hypersensitivity reactions can be IgE-mediated or non-IgE-mediated. Skin tests and specific IgE measurement unravel IgE-mediated reactions while BAT can be used for determining both IgE-mediated and non-IgE-mediated reactions [10]. The exclusion criterion was a previous history of allergic reactions to anaesthetic drugs. The patients were not taking steroid medication, H₁ or H₂ antihistamines or antidepressants.

In vivo tests, the SPT and the intradermal test (IDT), were performed using commercially available solutions of anaesthetic agents. Normal saline solution (0.9% NaCl) was used to dilute the commercial substances, as previously reported [11].

The tested substances included neuromuscular blocking agents: atracurium (Tracrium, Glaxo-Smith-Kline, Great Britain), pancuronium (Pavulon, Organon, Holland), rocuronium (Esmeron, Organon, Holland) and suxamethonium (Lysthenon, Nycomed, Austria), hypnotics: propofol (Propofol Lipuro, B.Braun Mesulgen AG, Germany), etomidate (Etomidat Lipuro, B.Braun Mesulgen AG, Germany), thiopental (Thiopental Sodium, Epico-Med SRL, Romania) and midazolam (Dormicum, Roche, Romania) and opioids: meperidine (Mialgin, Zentiva, Romania), fentanyl (Fentanyl Torrex, Torrex Chiesi Pharma GmbH, Austria) and remifentanyl (Ultiva, Glaxo-Smith-Kline, Great Britain). The maximal nonreactive concentrations used for the SPT and the IDT were those recommended by current guidelines of Société Française d'Anesthésie et Réanimation (SFAR), European Network of Drug Allergy, European Academy of Allergy and Clinical Immunology (EAACI). [3, 12] (Table 1).

The SPTs and IDTs were performed in conformity with international recommendations [3, 13], and according to the testing methodology described by authors with experience in skin testing [14]. We used 1% histamine as positive control and NaCl 0.9% as negative control. The SPT was considered positive when the wheal diameter was superior to 3 mm within 20 min. For IDT the wheal area was marked initially and 20 min after testing. An increase in diameter greater than 3 mm or a doubling of the initial injection wheal represented a positive result [3, 15].

For BAT, flow cytometric analysis of *in vitro* activated basophils was performed with the Flow2Cast technique (Bühlmann Laboratories AG, Switzerland). We used 14 test tubes containing 50 µl of whole blood. The blood was collected into K-EDTA venipuncture tubes, up to the dedi-

Table 1

Maximal nonreactive drug concentrations used for SPT, IDT and BAT

Anaesthetic agents	Maximal nonreactive drug concentrations SPT (mg ml ⁻¹)	IDT (µg ml ⁻¹)	Drug concentration BAT (µg ml ⁻¹)
Atracurium	10	10	2500
Rocuronium	10	100	500
Pancuronium	2	200	500
Suxamethonium	50	100	5
Propofol	10	1000	500
Etomidat	2	200	5
Thiopental	25	2500	2000
Fentanyl	0.05	5	5
Remifentanyl	0.05	5	5
Meperidine	25	2.5	2000
Midazolam	5	500	100

SPT, skin prick test; IDT, intradermal test; BAT, basophil activation test.

cated volume, from the antecubital vein (no tourniquet). The first sample was mixed with 50 µl of stimulation buffer as negative control. The next two samples were mixed with 50 µl solution of anti-FcRI (a highly specific monoclonal antibody for the IgE receptor) (Buhlmann Laboratory AG Schonenbuch, Switzerland) and 50 µl solution of FMLP (an unspecific cell activator- the chemotactic peptide N-Formyl- Met-Leu) (Buhlmann Laboratory AG Schonenbuch, Switzerland), as positive controls. In the remaining 11 test tubes, 50 µl of each anaesthetic drug solution was added. The maximal nonreactive drug concentrations are presented in Table 1. Subsequently, 20 µl staining reagent with two monoclonal antibodies, anti-CCR3-PE (human chemokine receptor labelled with phycoerythrin) (Buhlmann Laboratory AG Schonenbuch, Switzerland), and anti-CD63-FITC (Buhlmann Laboratory AG Schonenbuch, Switzerland) (or Gp53, a glycoprotein expressed on activated basophils), were added in each tube. The samples were incubated for 15 min at 37°C in a water bath. A pre-warmed lysing solution of 2 ml was added to each tube and incubated for 10 min at room temperature. After centrifuging (500 g, 5 min) and washing, the cells were suspended in 300 µl wash buffer (Buhlmann Laboratory AG Schonenbuch, Switzerland). The up-regulation of CD63 marker on the basophils was measured using the Cell Quest programme (FACSCalibur Becton Dickinson San Jose California USA Analyzer 2001). The result was considered positive when the percentage of activated basophils was 5% or more over spontaneous activation observed for the negative control or when the stimulation index calculated as the ratio between the percentage of activated basophils with the allergens and the negative control was ≥ 2 [16].

We detected drug-specific IgEs using 'sandwich'-type radio-immunoassay (RIA) with sepharose as solid phase (Pathologie Cellulaire et Moléculaire en Nutrition, Université Henri Poincaré, Nancy, France) and anti-IgEs I¹²⁵-

labelled antibodies (Immunotech, Prague, Czech Republic). Radioactivity was determined with a LKB gamma-counter (CliniGamma 1272-003, Wallac Oy, Finland). The result was considered positive when the binding of the patient IgEs on the solid phase (total γ radioactivity) was three times the negative control. For NMBAs, meperidine and midazolam we used quaternary ammonium-sepharose (QAS) as allergen for the first step (A = detected radioactivity in the first step). If the QAS antibodies were present, we performed an inhibition test with specific drugs in the second step (B = detected radioactivity in the second step). Inhibition (I) was estimated from the radioactivity adsorbed onto the sepharose in the first and the second step as $I = A - B/A \times 100$. The test was positive when the specific IgE binding radioactivity was modified by more than 20%.

All 40 patients were tested for the 11 anaesthetic drugs using SPT, IDT (which was restricted to those with a negative prick test), BAT and IgEs. From these tests, 440 overlapping observations were obtained.

The statistical analysis was performed using Excel software (2003, Microsoft Corporation, Seattle, USA). Chi-square test was used. A *P* value <0.05 was considered statistically significant.

Results

Out of the 40 patients, 34 (85%) were females. Information concerning gender, age, history of atopic disease, of uneventful general anaesthesia and drug allergy is presented in Table 2.

Of the 440 SPTs performed (11 substances in 40 patients) seven surpassed the positivity criterion (the prevalence of a positive SPT is 1.59%). Of these seven positive SPTs, six were for NMBAs and one for meperidine. Of our 40 patients, four presented with a positive SPT for NMBAs (the prevalence of patients with positive prick tests to NMBA is 10%) and two of them had a positive SPT for two different NMBAs. The positive SPTs for NMBAs were confirmed by BAT in five out of six of positive SPTs (83%). IgEs confirmed only two positive SPT with corresponding positive BAT. The only positive SPT for meperidine was not confirmed by any of the *in vitro* tests. For all anaesthetics, the result of the BAT agreed with the SPT in five out of seven positive SPTs (71%) and the result of IgEs agreed with the positive SPT in two out of seven positive SPTs (28%) (Table 3).

Four hundred and thirty-three IDTs were performed. Of these, 25 were positive (the prevalence of positive IDT is 5.77%). For NMBAs there were 10 positive IDTs. Only two of these were confirmed by BAT and three by IgEs. There were four positive tests for meperidine, one with a corresponding positive BAT. Of the 11 positive IDTs for midazolam none was confirmed by BAT. Of the 25 positive IDTs (for all anaesthetics), only three were confirmed by BAT (12%) and six by IgEs (24%) (Table 3).

Table 2

Patient personal data

Female	Age (years)	History of atopic diseases	Previous uneventful general anaesthesia	History of drug allergy		
				AB	Metamizol	AB and metamizol
34 (85%)	45.18 ± 24.80	10 (25%)	11 (27.5%)	18 (45%)	14 (35%)	8 (20%)

Age is expressed as medium age ± SD. AB, antibiotics.

Table 3*In vivo* and *in vitro* allergy tests results

Anaesthetic drug	Skin prick test			Intradermal test		
	Positive SPT	Positive BAT/ positive SPT	Positive IgEs/ positive SPT	Positive IDT	Positive BAT/ positive IDT	Positive IgEs/ positive IDT
Atracurium	2/40	2/2	0/2	4/38	0/4	2/4
Rocuronium	2/40	2/2	1/2	4/38	2/4	1/4
Pancuronium	0/40	0	0	1/40	0/1	0/1
Suxamethonium	2/40	1/2	1/2	1/38	0/1	0/1
Propofol	0/40	0	0	0/40	0	0
Etomidat	0/40	0	0	0/40	0	0
Thiopental	0/40	0	0	0/40	0	0
Fentanyl	0/40	0	0	0/40	0	0
Remifentanil	0/40	0	0	0/40	0	0
Meperidine	1/40	0/1	0/1	4/39	1/4	0/4
Midazolam	0/40	0	0	11/40	0/11	3/11

SPT, skin prick test; IDT, intradermal test; BAT, basophil activation test; IgEs, specific IgE antibodies.

There is a significant statistical difference between the concordance of positive BAT and positive SPT, 71% (five out of seven patients), much higher than the concordance of positive BAT and positive IDT, 12% (three out of 25 patients), (Chi-square tests, $P < 0.05$). There was no significant statistical difference between the concordance of RIA-IgEs and a positive SPT, 28% (two out of seven positive SPTs), and the concordance of RIA-IgEs and a positive IDT, 24% (six out of 25 positive IDTs), ($P > 0.05$).

Discussion

There is constant debate concerning the most valuable allergy test and the gold standard to diagnose or rule out allergy to a drug [17]. The lack of an infallible gold standard test is one of the major drawbacks of drug allergy tests. Prick and IDTs remain the reference of diagnosis with acceptable positive and predictive values for suspected drug allergy [18, 19], but their clinical predictive value in a patient without a history of anaesthetic drug allergy has not been established. The conclusion of many studies was that there were too many positive skin test results when screening for allergy to anaesthetic drugs in the general population. The prevalence of positive skin tests was much higher than the incidence of intra-anaesthetic anaphylaxis

[2, 6, 20]. The presence of a positive test might not only be a false positive test, but a proof of latent sensitization, with future possible subclinical or clinical expression (minor or major) [7]. Such presensitization, if true, should probably not be neglected since it has been demonstrated that for food or drug allergy, minor signs, often neglected, precede severe or lethal reactions [21]. Furthermore, there was a documented history of allergic reaction in only 28 of the 56 deaths due to anaphylactic shock (food, wasp venoms and drugs) [21]. Taken together, these results suggest that a previous history of allergy to anaesthetic drugs is either neglected or non-existent and that the dogma of performing allergy tests only to patients with a 'credible history' of allergy to that drug is not solid. On the other hand, the minor reactions during anaesthesia may not be recognized or reported and thus the total number of reported reactions may underestimate the real prevalence of the disease. In French studies the prevalence of latent sensitization to NMBA (skin and IgEs tests) varies between 1.6% in subjects without atopy and a drug allergy history to 16% in subjects with these risk factors [4].

Pholcodine, an opioid cough suppressant sharing an allergenic epitope with the NMBA, is incriminated in latent sensitization [22]. Johansson *et al.* found higher prevalence of IgE sensitization to pholcodine, morphine and suxamethonium after exposure to pholcodine-

containing cough mixture [23]. Withdrawal of pholcodine from the market significantly lowered, within 1–2 years, the levels of IgE antibodies to pholcodine, morphine and suxamethonium and within 3 years the frequency of NMBA-suspected anaphylaxis [24]. The quaternary ammonium ion (QAI) is the most likely allergen epitope to which an IgE antibody would be developed. However, other amines (tertiary structures like opioid derivatives) have been shown both to function as haptens and to be capable of inhibiting the QAI-specific reaction [25, 26]. In Romania, the cough suppressant agents also contain dextromethorphan, an opioid derivative that might lead to production of antibodies against substituted ammonia. Furthermore, the moment chosen for performing the tests for NMBAs, in relation to exposure to a substance that might induce the synthesis of anti ammonium antibodies can be important for the test results. It is known that pholcodine administration, in therapeutic doses, in subjects with a history of anaphylactic reaction to NMBAs, determined a great rise in antibody levels to pholcodine, morphine and suxamethonium [27]. Taken together, these results strongly support the hypothesis that complex mechanisms could underlie the presence of IgEs to anaesthetic drugs, thus explaining either the positive skin tests in previously unexposed individuals or cross reactions between different classes of drugs.

In our study, in a surgical population with a history of allergy to non-anaesthetic drugs, the prevalence of positive SPTs and IDTs to anaesthetics was 1.59% and 5.77% respectively.

Controversy persists as to the most valuable skin test. Prick tests are easy to perform, they are more suitable for children as they reduce pain and trauma and they have sensitivity and specificity above 95% [17]. Intradermal tests may be difficult to perform for the infrequent user and false positive results are more frequent than for SPTs [28]. The IDT is more sensitive than the SPT. However it also has a higher risk of inducing an irritative, false positive reaction when the drug is injected at too high concentrations [18]. There are also difficulties in interpretation because intrinsic histamine releasing activity is more marked on IDT, increasing the likelihood of false positive results [29].

Unlike Tamayo *et al.* we have performed not only SPTs for screening but also IDTs and *in vitro* tests, IgEs and BAT, to enforce the results of the SPTs [1]. BAT might provide additional information as the technique closely resembles the *in vivo* pathway leading to symptoms [30].

In our series, the prevalence of positive SPTs (1.59%) was lower than the prevalence of positive IDT (5.77%), but skin prick sensitivity was confirmed by BAT in most cases (71.42%), whereas only a low percentage of positive IDTs was confirmed (12%). Of the six positive SPTs to NMBAs, five had a corresponding positive BAT, two of them with positive IgEs, suggesting theoretically IgE-mediated hypersensitivity, and three of them with negative IgEs, which might suggest non-IgE-mediated hypersensitivity or the

presence of drug antibodies other than those detected by RIA. Four patients out of 40 presented with a positive SPT for NMBAs and two of them had a positive SPT from two different NMBAs confirming the cross reactivity for NMBAs.

The low rate of confirmation of positive IDTs (especially for midazolam and meperidine) both through flow cytometric analysis and IgE quantification suggests that there is a risk of false positive results with IDTs. The fact that such false positive reactions are not uncommon has been previously stated [17], and the maximal nonreactive concentration for midazolam was found to be lower than that considered by SFAR and EAACI [11]. Even though the incidence of midazolam allergy is low [12], in daily practice midazolam is also tested as an alternative compound. The high prevalence of positive IDTs with negative BATs and IgEs in our series may be the result of a too high midazolam concentration [11]. Intradermal tests are prone to false positive results when too high concentrations are used, on the other hand using too low a concentration is a source of false negative results. In the context of anaesthesia allergy a false positive result is less dangerous than a false negative result. The issue is to avoid both false positive and false negative reactions [31].

The maximal nonreactive concentrations for IDTs need to be adequately defined for some anaesthetic drugs, as long as the NMBAs have been extensively studied [12, 32, 33].

In our study, the prevalence of patients with a positive SPT to NMBAs was higher (10%) than that reported in general population (2.8%–4.65%) [1, 6]. Nevertheless, in our study, a high percentage of positive SPTs with a high rate of confirmation through BAT, suggests that a prior history of allergy to non-anaesthetic drugs might predict positive prick tests to anaesthetic drugs. The concordance between a positive SPT and a positive BAT was the highest. The reliability of BAT as a predictive tool requires further research as the power of our study was limited by the number of overlapped tests (440).

Given the known limitations of *in vivo* and *in vitro* drug allergy tests, the question is whether our results represent a true or false positive. In case our results are false positive, there might be a need for reconsidering the maximal non-reactive concentrations used for IDTs. Furthermore, the optimal concentrations for anaesthetic drugs have not yet been fully validated for BAT [4].

If the results are true, the questions concern the mechanisms and the potential clinical implications. As for the mechanisms, the pholcodine story provides a credible explanation for cross reactivity and sensitization. Furthermore, it is possible that some patients, through multiple mechanisms, are at higher risk of developing allergic reactions to multiple antigens. This is consistent with the above-mentioned publication that showed a much higher prevalence of positive skin tests to NMBAs in patients with atopy [4]. In the latest French recommendations (2011) for good clinical practice regarding peri-anaesthetic

anaphylaxis it was shown that in the history of the patients with NMBA-induced anaphylaxis, the allergy to penicillines was frequently identified [34]. In our allergeo-anaesthesia centre 41% of the patients with peri-anaesthetic anaphylaxis had self-reported drug allergy, especially for antibiotics (data not published yet).

What could be the clinical implications of our study findings? The international recommendations are to direct to allergy specialists only patients with a credible history of allergy to the culprit drug. Routine clinical practice, nevertheless, demonstrates that this is not the rule and many allergy specialists do 'screen' for allergy to anaesthetic drugs. Moreover the SPTs are not expensive or time consuming and there was no evidence of NMBA sensitization produced by skin tests, as evidenced by the lack of histamine release in blood samples collected at the follow-up visit in the 29 volunteers studied [32]. In this case, the question is what should one do in a patient with a positive skin test to some NMBAs, confirmed by *in vitro* tests? Because we cannot exclude the existence of latent sensitization reactions that might lead to future minor or major clinical expression, avoidance of the drug for which the tests were positive could be recommended. Fortunately none of our patients were positive for all tested NMBAs and thus 'a safe' NMBA can always be chosen for further anaesthesia. Similarly, in clinical practice, when skin testing is carried out to a wide range of peri-anaesthetic drugs, and positive skin tests to NMBAs (not administered at the time of the anaphylactic reaction) are identified, they should be identified as a potential risk [28] and avoidance recommended, even though the significance is not known.

In conclusion, in a selected population with a history of allergy to non-anaesthetic drugs the prevalence of positive NMBA prick tests and of positive NMBA specific IgEs is higher than that documented in the surgical population. The percentage of positive IDTs to midazolam is too high taking into account that this substance is rarely involved in peri-anaesthetic anaphylaxis. The results could be explained by latent sensitization for NMBAs or false positive results for midazolam. These results, whether reflecting true allergy or test inaccuracies, should be taken into consideration when interpreting allergy tests to anaesthetic drugs. High prevalence of positive *in vivo* and *in vitro* allergy tests to NMBAs in our study population with a prior history of allergy to non-anaesthetic drugs could be an argument for a pre-operative SPT to NMBAs for this surgical population. A larger prospective study is needed to validate our results, especially for NMBAs which have the highest prevalence of positive SPTs and BATs and the highest risk for anaesthesia anaphylaxis.

Competing Interests

There are no competing interests to declare.

The financial support from the National Plan II, Priority Domain Partnership Romania, under number 41-062/2007, was highly appreciated.

REFERENCES

- 1 Tamayo E, Alvarez FJ, Rodriguez-Ceron G, Gomez-Herreras JI, Castrodeza J. Prevalence of positive prick test to anaesthetic drugs in the surgical population. *Allergy* 2006; 61: 952-3.
- 2 Porri F, Pradal M, Rud C, Alazia M, Gouin F, Vervloet D. Is systematic preoperative screening for muscle relaxant and latex allergy advisable? *Allergy* 1995; 50: 374-7.
- 3 Mertes PM, Laxenaire MC, Lienhart A, the working group of the SFAR, Aberer W, Ring J, Pichler WJ, Demoly P, for ENDA and the EAACI interest group on drug hypersensitivity. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2005; 15: 91-101.
- 4 Mertes PM, Aimone-Gastin I, Gueant-Rodriguez RM. Hypersensitivity reactions to neuromuscular blocking agents. *Curr Pharm Des* 2008; 14: 2809-25.
- 5 Tamayo E, Alvarez FJ, Rodriguez-Ceron G, Gomez-Herreras JI, Castrodeza J. Prevalence of positive prick tests to neuromuscular blocking drugs in the surgical population. *Br J Clin Pharmacol* 2006; 62: 506-7.
- 6 Porri F, Lemiere C, Birnbaum J, Guilloux L, Lanteaume A, Didelot R, Charpin D, Vervloet D. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy* 1999; 29: 72-5.
- 7 Moneret-Vautrin DA, Renaudin JM, Kanny G, Widler S, Hanesse B, Dezfoulan B. Prospective study of the latent sensitization to muscle relaxants. In: *Progress in Allergy and Clinical Immunology*, eds Dehling AK, Huerat-Lopez JG. Cancun: Hogrefe and Huber, 1997; 361-76.
- 8 Florvaag E, Johansson SGO, Oman H, Venemalm L, Degerbeck F, Dybendal T, Lundberg M. Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. *Acta Anaesthesiol Scand* 2005; 49: 437-44.
- 9 Gamboa PM, Sanz ML, Caballero MR, Antepara I, Urrutia I, Jauregui I, Gonzalez G, Dieguez I, De Weck AL. Use of CD63 expression as a marker of *in vitro* basophil activation and leukotriene determination in metamizol allergic patients. *Allergy* 2003; 58: 312-17.
- 10 Sanz ML, Gamboa PM, De Weck AL. Cellular tests in the diagnosis of drug hypersensitivity. *Curr Pharm Des* 2008; 14: 2803-8.
- 11 Hagau N, Bologa R, Indrei C, Longrois D, Dirzu D, Gherman-Ionica N. The maximum non-reactive concentration of midazolam and ketamine for skin testing study in non-allergic healthy volunteers. *Anaesth Intensive Care* 2010; 38: 513-18.
- 12 Ebo DG, Fisher MM, Hagedorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; 62: 471-87.

- 13 Kroigaard M, Garvey LH, Gillberg L, Johansson SGO, Mosbech H, Florvaag E, Harboe T, Eriksson LI, Dahlgren G, Seeman-Lodding H, Takala R, Wattwil M, Hirlekar G, Dahlén B, Guttormsen AB. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; 51: 655–70.
- 14 Demoly P, Piette V, Bousquet J. *In vivo* methods for study of allergy: skin tests, technique and interpretation. In: Middleton's Allergy, Principles and Practice, 6th edn. eds Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate TS, Simons FER. Philadelphia, PA: Mosby, Inc., 2003; 631–43.
- 15 Brockow K, Romano A, Blanca M, Ring I, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; 57: 45–51.
- 16 Gamboa PM, Garcia-Aviles MC, Urrutia I, Antepara I, Esparza R, Sanz ML. Basophil activation and sulfidoleukotriene production in patients with immediate allergy to betalactam antibiotics and negative skin tests. *J Investig Allergol Clin Immunol* 2004; 14: 278–83.
- 17 Bleasel K, Donnan G, Unglik G. General anesthetic allergy testing. *Curr Allergy Asthma Rep* 2009; 9: 50–6.
- 18 Brockow K, Romano A. Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des* 2008; 14: 2778–91.
- 19 Lavaud F, Mouton C, Ponvert C. Les tests cutanes dans le bilan diagnostique des reactions d'hypersensibilite peranesthesiques. Skin tests to diagnose hypersensitivity reactions occurring during anaesthesia. *Ann Fr Anesth Reanim* 2011; 30: 264–79.
- 20 Maria Y, Grosdidier R, Haberer JP, Moneret-Vautrin DA. Enquête prospective préopératoire chez 300 patients par prick-tests aux myorelaxants. *Ann Fr Anesth Reanim* 1989; 8: 301–5.
- 21 Pumphrey RSH, Roberts ISD. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000; 53: 273–6.
- 22 Florvaag E, Johansson SG. IgE-mediated anaphylactic reactions to neuromuscular blocking agents: can they be prevented? *Curr Allergy Asthma Rep* 2008; 8: 365–76.
- 23 Johansson SGO, Florvaag E, Oman H, Poulsen LK, Mertes PM, Harper NJN, Garvey LH, Gerth van Wijk R, Metso T, Irgens A, Dybendal T, Halsey J, Seneviratne SL, Guttormsen AB. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. *Allergy* 2010; 65: 498–502.
- 24 Florvaag E, Johansson SGO, Irgens A, de Pater GH. IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. *Allergy* 2010; 66: 955–60.
- 25 Baldo BA, Fisher MM. Anaphylaxis to muscle relaxant drugs: cross-reactivity and molecular basis of binding of IgE antibodies detected by radioimmunoassay. *Mol Immunol* 1983; 20: 1393–400.
- 26 Baldo BA, Fisher MM, Pham NH. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. *Clin Exp Allergy* 2009; 39: 325–44.
- 27 Harboe T, Johansson SG, Florvaag E, Oman H. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. *Allergy* 2007; 62: 1445–50.
- 28 Moneret-Vautrin DA, Laxenaire MC, Widmwr S, Hummer M. The value of prick tests in the detection of anaphylaxis caused by muscle relaxants. *Ann Fr Anesth Reanim* 1987; 6: 352–5.
- 29 Ewan PW, Dugue P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy* 2009; 40: 15–31.
- 30 Ebo D, Bridts C, Hagendorens M, Aerts N, De Clerck L, Stevens W. Basophil activation test by flow cytometry: present and future applications in allergology. *Clin Cytom* 2008; 74B: 201–10.
- 31 Fisher MM, Doig GS. Prevention of anaphylactic reactions to anaesthetic drugs. *Drug Saf* 2004; 27: 393–410.
- 32 Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000; 85: 844–9.
- 33 Mertes PM, Moneret-Vautrin DA, Leynadier F, Laxenaire MC. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. *Anesthesiology* 2007; 107: 245–52.
- 34 Moneret-Vautrin D-A, Codreanu F, Drouet M, Plaud B, Karila C, Valfrey J, Debaene B, Malinovsky J-M, Mertes J-M. Conduite a tenir de l'anesthésiste en cas de reaction medicamenteuse anterieure Allergologic screening and management of patients with previous self-reported hypersensitivity reactions. *Ann Fr Anesth Reanim* 2011; 30: 246–63.