



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Original article

Antibiotic-induced immediate type hypersensitivity is a risk factor for positive allergy skin tests for neuromuscular blocking agents

Natalia Hagau^{a,*}, Nadia Gherman^b, Mihaela Cocis^a, Cristina Petrisor^a^a Department of Anaesthesia and Intensive Care II, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania^b Department of Allergy and Immunology, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

ARTICLE INFO

Article history:

Received 16 January 2015

Received in revised form

8 June 2015

Accepted 21 July 2015

Available online xxx

Keywords:

Antibiotic

Drug hypersensitivity

Latent sensitization

Neuromuscular blocking agent

Skin tests

Abbreviations:

NMBAs	neuromuscular blocking agents
SPT	skin prick test
IDT	intradermal test
RW	reading wheal for the intradermal test
IW	injection wheal for the intradermal test

ABSTRACT

Background: Skin tests for neuromuscular blocking agents (NMBAs) are not currently recommended for the general population undergoing general anaesthesia. In a previous study we have reported a high incidence of positive allergy tests for NMBAs in patients with a positive history of non-anaesthetic drug allergy, a larger prospective study being needed to confirm those preliminary results. The objective of this study was to compare the skin tests results for patients with a positive history of antibiotic-induced immediate type hypersensitivity reactions to those of controls without drug allergies.

Methods: Ninety eight patients with previous antibiotic hypersensitivity and 72 controls were prospectively included. Skin tests were performed for atracurium, pancuronium, rocuronium, and suxamethonium.

Results: We found 65 positive skin tests from the 392 tests performed in patients with a positive history of antibiotic hypersensitivity (16.58%) and 23 positive skin tests from the 288 performed in controls (7.98%), the two incidences showing significant statistical difference ($p = 0.0011$). The relative risk for having a positive skin test for NMBAs for patients *versus* controls was 1.77 (1.15–2.76). For atracurium, skin tests were more often positive in patients with a positive history of antibiotic hypersensitivity *versus* controls ($p = 0.02$). For pancuronium, rocuronium and suxamethonium the statistical difference was not attained (p -values 0.08 for pancuronium, 0.23 for rocuronium, and 0.26 for suxamethonium).

Conclusions: Patients with a positive history of antibiotic hypersensitivity seem to have a higher incidence of positive skin tests for NMBAs. They might represent a group at higher risk for developing intraoperative anaphylaxis compared to the general population.

Copyright © 2015, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The identification of risk factors for drug hypersensitivity may define categories of patients who are at risk after drug exposure and may allow the avoidance of certain drugs in patients with previous sensitization by performing an appropriate allergological screening. Current epidemiological studies indicate both exposure characteristics, host and drug factors, including sex, age and possibly atopy, as representing such risk factors, though there is no definitive consensus regarding some of them.^{1,2}

Neuromuscular blocking agents (NMBAs) are the drugs most often incriminated in intraanaesthetic anaphylaxis. Allergological

skin tests for NMBAs are not currently recommended for the general population undergoing general anaesthesia.^{3–5} However, in a previous study we have reported a high prevalence of positive *in vivo* and *in vitro* allergy tests for NMBAs in patients with a positive history of non-anaesthetic drug allergy and hypothesized that preoperative testing for NMBAs might be necessary in this category of patients.⁶ Screening tests for anaesthetic drugs might prove valuable when a defined risk profile is selected, larger prospective studies being needed to confirm those preliminary results and validate changes in clinical anaesthesiology and allergology practice.⁶

The objective of the study was to compare the skin tests results for a high number of patients with a positive history of antibiotic-induced hypersensitivity reactions to those of controls without previous drug allergies and to establish whether antibiotic hypersensitivity and atopy are risk factors for positive skin tests to NMBAs.

* Corresponding author. Department of Anaesthesia and Intensive Care, Clinical Emergency County Hospital of Cluj, 400006 Clinicilor 3–5, Cluj-Napoca, Romania.

E-mail address: hagaunatalia@gmail.com (N. Hagau).

Peer review under responsibility of Japanese Society of Allergy.

<http://dx.doi.org/10.1016/j.alit.2015.07.007>

1323–8930/Copyright © 2015, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Methods

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy “Iuliu Hatieganu” Cluj-Napoca (no.6/2008). We included in this prospective study 98 consecutive patients with previous signs and symptoms suggestive for antibiotic-induced immediate-type hypersensitivity reactions ranging from urticaria, angioedema, and bronchospasm, to severe hypotension or cardiac arrest. The patients were referred to the allergy unit for testing by the general practitioners or anaesthesiologists as they required to undergo elective surgery under general anaesthesia. Each patient completed, guided by an allergologist, a structured questionnaire containing data regarding the date of the clinical reactions, the signs and symptoms, current medication and comorbidities. All patients presented positive skin tests for the culprit antibiotics (either the skin prick test or the intradermal test). A number of 72 healthy controls, people without any previous drug hypersensitivity, nor positive skin tests, were included as well. Exclusion criteria were: a positive history of hypersensitivity to drugs others than antibiotics, treatment with steroids or antihistamines, dermographism and pregnancy. All patients and controls were informed verbally and in written about the study and signed the informed consent form.

Skin tests included the skin prick test (SPT) and the intradermal test (IDT) and were performed according to international recommendations for atracurium (Tracrium[®], Glaxo-Smith-Kline, Great Britain), pancuronium (Pavulon[®], Organon, Holland), rocuronium (Esmeron[®], Organon, Holland), and suxamethonium (Lysthenon[®], Nycomed, Austria) for each patient and control. The allergologist was blinded regarding the patients' hypersensitivity history. We used 1% histamine as positive control and 0.9% NaCl as negative controls. The skin tests were performed using commercially available drug solutions for intravenous use, which were diluted with 0.9% NaCl to obtain the currently recommended dilutions for testing (Table 1).^{7–9} The skin tests were performed on the anterior region of the forearm. For the SPT, a drop of the drug solution was placed and the skin was pricked with a prick needle in the centre of the drop. For the IDT, 0.02–0.03 mL of drug solution was injected using a 29.5 gauge needle, producing a 4 mm injection wheal. The SPT was considered positive when the wheal diameter was ≥ 3 mm at 20 min, while the IDT was considered positive if the reading wheal (RW) doubled the injection wheal (IW) at 20 min (the RW/IW ratio ≥ 2).^{7,9} First, the SPT was performed. When the SPT was

negative, the IDT was performed subsequently and if the SPT was positive, the IDT was not performed. The skin test result was considered positive when either the SPT or the IDT were positive, and negative when neither of these were positive.

The atopic phenotype status was recorded according to the patients' report of previous atopic diseases like allergic rhinitis with nasal symptoms, allergic asthma, acute and chronic urticaria and/or atopic dermatitis.

Chi square tests and Fisher exact test were used to assess the differences between categorical data. Relative risk was calculated as $a/(a + b)/c/(c + d)$, where a = number of patients with previous antibiotic hypersensitivity with positive skin tests for NMBAs, b = number of patients with previous antibiotic hypersensitivity and negative skin tests for NMBAs, c = number of controls with positive skin tests for NMBAs, and d = number of controls with negative skin tests for NMBAs.

Results

A total of 98 patients with previous antibiotic-induced immediate type hypersensitivity reactions were tested using the SPT and the IDT for atracurium, rocuronium, pancuronium and suxamethonium, thus we performed 392 tests for NMBAs. The culprit antibiotics were penicillins in 83 patients (84.69%): penicillin in 37 patients, ampicillin in 18, amoxicillin in 13, oxacillin in 1, piperacillin in 1 and two or more penicillins in 14 patients. In the remaining 15 patients (15.30%), the culprit drugs were cephalosporins in 5 patients (cefaclor 1, ceftriaxone 1 and cefuroxime 3 patients), trimetoprim-sulphamethoxazole in 1 patient, quinolones in 6 patients, metronidazole in one and erythromycin in one patient. All patients presented positive skin tests for the culprit drugs. We also tested 72 healthy controls without previous drug-induced immediate-type hypersensitivity reactions for the same NMBAs, which represents a total of 288 tests performed in controls. From the 392 skin tests performed in patients with antibiotic hypersensitivity, we found 9 positive SPT and 56 positive IDT in 46 out of the 98 patients (46.93%). From the 288 skin tests performed in controls, we found 23 positive IDT in 19 out of the 72 healthy controls (26.38%). Thus, we found 65 positive skin tests from the 392 tests performed in patients with a positive history of antibiotic hypersensitivity (16.58%) and 23 positive skin tests from the 288 performed in controls (7.98%), the two incidences showing significant statistical difference (Chi squared test, $p = 0.0011$) (Table 2).

Table 1
Maximal non-reactive NMBAs concentrations used for the skin tests.

NMBA	Undiluted drug (mg/mL)	SPT		IDT	
		Dilution	Concentration (mg/mL)	Dilution	Concentration (μ g/mL)
Atracurium	10	1/10	1	1/1000	10
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/100	100
Suxamethonium	50	1/5	10	1/500	100

NMBA, neuromuscular blocking agent; SPT, skin prick test; IDT, intradermal test.

Table 2
Skin test results for NMBAs.

	No. patients	No. tests	Atopic disease	Atracurium		Pancuronium		Rocuronium		Suxamethonium	
				SPT	IDT	SPT	IDT	SPT	IDT	SPT	IDT
Patients with positive history	98	392	Present (N = 20)	1/20	6/19	1/20	3/19	0/20	2/20	2/20	1/18
			Absent (N = 78)	4/78	28/74	0/78	4/78	1/78	12/77	0/78	0/78
Controls	72	288	Present (N = 37)	0/37	14/37	0/37	1/37	0/37	3/37	0/37	0/37
			Absent (N = 35)	0/35	2/35	0/35	0/35	0/35	3/35	0/35	0/35

SPT, skin prick test; IDT, intradermal test; No, number.

The relative risk for having a positive skin test for NMBAs for patients *versus* controls was 1.77 (95%CI: 1.15–2.76).

When each NMBA was considered, for atracurium, skin tests were more often positive in patients with a positive history of antibiotic hypersensitivity when compared to controls (Fisher test, $p = 0.02$), while for pancuronium, rocuronium and suxamethonium the statistical difference was not attained (Fisher test, p -values 0.08 for pancuronium, 0.23 for rocuronium, and 0.26 for suxamethonium). From the four tested NMBAs, the highest number of positive skin tests was observed for atracurium (Table 2).

From the 98 patients, 9 had previously undergone surgery under general anaesthesia using NMBAs, with no adverse reactions. Four patients from these presented positive skin tests for NMBAs. Eleven controls, from which 3 with demonstrating positive skin tests for NMBAs, had previous uneventful exposure to NMBAs during general anaesthesia.

After testing, all the patients underwent surgery under general anaesthesia using the NMBAs for which the skin tests were negative. Anaesthesia was uneventful in all subjects by avoiding the NMBAs for which the skin test was positive in the patients with positive skin tests. None of the patients with previous antibiotic-induced hypersensitivity reactions presented positive skin tests for all the tested NMBAs.

From the 98 patients (82 female and 16 male patients), 20 (20.40%) declared having an atopic phenotype. From the 72 controls, 37 declared having an atopic phenotype. Thus, we tested 57 subjects with atopy and 113 subjects without atopy. We performed a total number of 228 skin tests in subjects (patients with previous antibiotic hypersensitivity and controls) that presented in the history atopic diseases, with 34 of them having positive skin tests results (14.91%). For those without atopic disease, we performed a total number of 452 skin tests for NMBAs, 54 of them being positive (11.94%). There is no statistical difference between those with and without atopic disease regarding the positivity of the skin tests' results (Chi square, $p = 0.28$).

From the 130 females tested, a number of 51 (39.23%) presented positive skin tests for NMBAs, while from the 40 males tested, a number of 14 (35%) presented positive skin tests for NMBAs (Chi square, $p = 0.087$).

Discussion

Both drug and host factors, including sex, age, and genetic predisposition, together with characteristics of the drug exposure, interact in the development of drug allergy.¹ The performance of screening tests might be justified for well-defined at-risk categories of patients for which certain drugs could be avoided.

NMBAs are the leading drugs responsible for immediate hypersensitivity reactions during anaesthesia, but there is no demonstrated evidence supporting systematic pre-operative screening in the general population at this time.³ Skin tests should not be used to screen for drug allergy in the absence of clinical history compatible with allergy.^{4,8,10,11}

Although there is no demonstrated evidence for systematic pre-operative screening in the general population, well-defined at-risk patients might benefit from the performance of screening tests.³ In the past, some authors stipulated that there is no evidence of increased risk of anaphylaxis to NMBAs in patients who have had anaphylaxis to drugs not used in the operating theatre and in patients presenting atopic disease.¹² However, there have been previous reports showing a high prevalence of skin tests for NMBAs in patients with other drug-induced immediate-type hypersensitivity reactions.^{13,14} Similarly, we have previously reported a high prevalence of positive *in vivo* and *in vitro* tests for NMBAs in patients with a positive history of non-anaesthetic drug-induced

immediate-type hypersensitivity reactions and larger, prospective studies are needed.⁶

In drug allergy, skin testing is the most widely used method to determine sensitization, as other tests are less sensitive and less specific.⁸ In this study we found that the patients with a positive history of antibiotic hypersensitivity have a higher risk to present a positive skin tests for NMBAs when screening skin tests are performed. Positive skin tests might be the result of sensitization, local histamine release or the use of irritative drug concentrations for skin testing.

The fact that some of the healthy controls also presented positive skin tests can be argued by the occurrence of latent sensitization after exposure to cross-reactive compounds. Sensitization may be caused by previous exposure to foods, cosmetics, disinfectants and industrial materials containing quaternary substituted ammonium ions in their structure.³

Moreover, we found different positivity rates for the four NMBAs we tested. The highest number of positive skin tests was observed for atracurium, a drug known to cause direct local histamine release when skin tests are performed. The maximal nonreactive concentrations for IDT need to be adequately defined for anaesthetic drugs.^{15–17} False positive results might be avoided by the use of adequately defined testing concentrations as some of the NMBAs cause local histamine release.^{8,10} For atracurium, the high incidence of positive intradermal tests might be related to increased local histamine release or suggests that the recommended test doses might be too high.

A limitation of our study is the fact that the positive predictive value of skin tests with NMBAs is unknown.¹⁸ A positive skin test does not mean that the patient is going to develop allergic reactions upon exposure. The progression from a positive allergy test to clinical allergy is multifactorial, and the presence of a positive skin test might be a proof of latent sensitization, with possible sub-clinical, minor or major clinical reaction.¹⁹ The prevalence of latent sensitization to NMBAs (skin tests and drug specific IgE dosing) was shown to vary between 1.6% in subjects without atopy or a drug allergy history to 16% in subjects with these risk factors.¹⁹ Sensitization might be a necessary preliminary condition for anaphylaxis to appear clinically and patients with latent sensitization, assessed here by allergological skin tests, might represent a group of patients at high risk for developing intraanaesthetic anaphylaxis due to exposure to NMBAs. Patients with a positive history of antibiotic-induced immediate type hypersensitivity reactions might represent a group at higher risk for developing intraoperative anaphylaxis compared to the general population. This risk can not yet be evaluated as the predictive value of positive skin tests results is unknown.

There is no definitive agreement whether the presence of the atopic phenotype is a risk factor for drug hypersensitivity in general.^{1,2,10,20} In our patients, the presence of the atopic phenotype was not demonstrated as being a risk factor for having a positive skin test to NMBAs. Our study reinforces other epidemiological data on self-reported drug-induced hypersensitivity reactions, which are more often in females.² However, we concluded that gender per se is not a risk factor for positive skin tests for NMBAs.

In conclusion, a positive history of antibiotic-induced immediate type hypersensitivity is predictive for positive skin tests for NMBAs.

Acknowledgements

The financial support from the National Plan II, Priority Domain Partnership Romania, under number 41-062/2007, was appreciated. A subset of the patients have been reported in a previous

paper representing a preliminary study regarding screening tests for anaesthetic drugs.⁶

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

NH designed the present study, contributed to the acquisition of data, the analysis and the interpretation of data, and has been involved in drafting the manuscript. NG performed the allergological tests, has participated in data acquisition and revised the manuscript. MC has participated in data acquisition and analysis and revised the manuscript. CP has participated in data acquisition, data analysis and interpretation and has been involved in drafting the manuscript. All authors read and approved the final manuscript.

References

1. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;**105**:259–73.
2. Thong B, Tan T. Epidemiology and risk factors for drug allergy. *Br J Clin Pharm* 2011;**71**:684–700.
3. Mertes PM, Aimone-Gastin I, Gueant-Rodriguez RM, Mouton-Faivre C, Audibert G, O'Brien J, et al. Hypersensitivity reactions to neuromuscular blocking agents. *Curr Pharm Des* 2008;**14**:2809–25.
4. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, et al., Working Group for the SFAR; ENDA; 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.
5. Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007;**51**:655–70.
6. Hagau N, Gherman-Ionica N, Hagau D, Tranca S, Sfichi M, Longrois D. Is a positive history of non-anaesthetic drug allergy a predictive factor for positive allergy tests to anaesthetics? *Br J Clin Pharmacol* 2011;**73**:460–6.
7. Demoly P, Piette V, Bousquet J. In vivo methods for study of allergy: skin tests, technique and interpretation. In: Adkinson Jr NF, Yunginger JW, Busse WW, Bochner BS, Holgate TS, Simons FER, editors. *Middleton's Allergy, Principles and Practice*. 6th ed. Philadelphia: Mosby; 2003. p. 631–43.
8. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Group position paper. *Allergy* 2013;**68**:702–12.
9. Mertes PM, Tajima K, Regnier-Kimmon MA, Lambert M, Iohom G, Guéant-Rodriguez RM, et al. Perioperative anaphylaxis. *Med Clin North Am* 2010;**94**:761–89.
10. Mirakian R, Ewan PW, Durham SR, Youtren LJF, Dugue P, Friedmann PS, et al. BSACI guidelines for the management of drug allergy. *Clin Exp Allergy* 2009;**39**:43–61.
11. 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.
12. Mertes PM, Malinovsky JM, Jouffroy L, Working Group of the SFAR and SFA, Aberer W, Terreehorst I, et al. Reducing the risk of anaphylaxis during anaesthesia: 2011 updated guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2011;**21**:442–53.
13. Tamayo E, Rodriguez-Ceron G, Gomez-Herreras JI, Fernandez A, Castrodeza J, Alvarez FJ. Prick-test evaluation to anaesthetics in patients attending a general allergy clinic. *Eur J Anaesth* 2006;**23**:1031–6.
14. 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.
15. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007;**62**:471–87.
16. 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.
17. 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.
18. Abuaf N, Rajoely B, Ghazouani E, Levy DA, Pecquet C, Chabane H, et al. Validation of a flow cytometric assay detecting in vitro basophil activation for the diagnosis of muscle relaxant allergy. *J Allergy Clin Immunol* 1999;**104**:411–8.
19. Moneret-Vautrin DA, Renaudin JM, Kanny G, Widler S, Hanesse B, Dezfoulian B. Prospective study of the latent sensitization to muscle relaxants. In: Dehling AK, Huerat-Lopez JG, editors. *Progress in Allergy and Clinical Immunology*. Cancun: Hogrefe and Huber; 1997. p. 361–76.
20. Warrington R, Silviu-Dan F. Drug allergy. *Allergy, Asthma Clin Immunol* 2011;**7**(Suppl 1):S10.