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Original article

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

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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 (1 6.58%) 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.

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.

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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 categorial 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), trimetroprim-sulphametoxazole 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 (μg/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.