

Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening

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Summary

Background Muscle relaxants (MR) are responsible for 59% of peroperative anaphylactic reactions. A major issue would be to determine whether a systematic preoperative screening in the general population should be recommended.

Objective The purpose of the study was to evaluate the prevalence of muscle relaxant sensitivity in a sample of the general population and to assess the role of possible risk factors.

Methods Two hundred and fifty-eight subjects, aged 20–40 years, visiting a health care centre for a check-up were evaluated. Protocol included a questionnaire (occupation, symptoms of atopy, previous surgery, history of drug allergy), skin-prick tests to four commercial muscle relaxants and measurement of specific IgE against quaternary ammonium ions. Atopy was evaluated by skin-prick tests to common inhalant allergens and by a Phadiatop test.

Results Of the study group, 9.3% had either a positive skin test to one or more muscle relaxant or a presence of specific IgE to quaternary ammonium ions. No risk factor was identified in the studied group.

Conclusion Since the rate of MR sensitivity is much higher than the anticipated rate of peroperative reactions due to allergy, a systematic preoperative screening for MR allergy should not be recommended for adults in a general population.

Keywords: muscle relaxants, prevalence, screening, drug hypersensitivity, risk factors

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Introduction

Muscle relaxants (MR) are responsible for 59% of peroperative anaphylactic reactions in adult patients in France [1]. The only risk factor recognized is female gender, with 75% of reactions occurring in women [2]. Other risk factors proposed have been atopy, history of previous general anaesthetics (GA) and number of GA, but have not been proved. Moneret-Vautrin *et al.* tested 147 subjects, including five with history of allergy to MR, with five MR, and found all tests negative [3].

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More recently in a study including subjects without risk factors, the same group found 1.6% of sensitivity [4]. Prior to proposing a systematic preoperative screening for MR sensitivity, it is necessary to know the rate of sensitivity in the general population to determine the predictive value of MR sensitivity for the occurrence of peroperative anaphylactic reactions. Since a number of studies have demonstrated either the usefulness of skin tests to retrospectively confirm allergy to MR and the possibility of detecting specific IgE to quaternary ammonium ions (the major allergenic epitopes of MR) in the serum [2,5] the aim of our study was to evaluate the rate of MR sensitivity in a group of subjects visiting a health care centre for a check-up examination, and the possible risk factors influencing this rate.

Methods

The population study included 747 subjects 20–40 years old visiting a health care centre for a check-up. This examination is provided by the National Health Service on a 5-yearly basis to all those affiliated, i.e. 95% of the general population. The protocol included a questionnaire about occupation, symptoms of atopy, number of previous surgical procedures, reactions occurring during surgery and possible history of drug allergy. Patients were considered to be clinically atopic if they answered yes to at least one of the following questions: 'Have you ever had hay fever?', 'Do you usually have rhinitis or nasal obstruction?', 'Have you ever had asthma?'. Only 258 subjects agreed to undergo skin tests and blood sampling for measurement of specific IgE against quaternary ammonium ions. Skin-prick tests were performed with common inhalant allergens and four MR.

Common inhalant allergens tested were commercial extracts (Stallergenes Co) standardized in terms of biological units ('reactivity index' = RI) or only in terms of weight/volume (w/v), using the following allergens: *Dermatophagoides pteronyssinus* (100 RI/mL), cypress (1/20 w/v), grass pollen (100 RI/mL), parietaria (100 RI/mL), alternaria (100 RI/mL) and cat dander (100 RI/mL).

MR tested with the prick technique were approximately 1/10 diluted solution of atracurium (1 mg/mL) and non-diluted solutions of vecuronium (4 mg/mL) pancuronium (2 mg/mL) and suxamethonium (10 mg/mL). These concentrations were chosen according to previous work studying correlation between intradermic tests and prick tests [6]. The positive control was a 9% codeine phosphate solution and the negative control was the allergen diluent. Weal diameter was recorded 20 min later. Prick tests were considered to be positive if the weal measured was 3 mm larger than the weal of the negative control. Blood sampling was also performed to measure specific IgE to a group of common inhalant allergens (Phadiatop, Pharmacia, Sweden), and specific IgE directed toward quaternary ammonium ions. In our study we used the PAPPC-RAST [7]. The solid-phase complex is p-aminophenyl phosphoryl choline immobilized on agarose and RIA was performed with an antihuman IgE labelled with ^{125}I . Results were given as percentage of radioactivity. This technique assays the presence of specific IgE antibodies against quaternary ammonium ions which are known to be the major muscle relaxants allergenic epitopes [5]. The threshold of positivity for the IgE measurement was set at 0.35 kU/L (class 1). Atopy was diagnosed by the presence of one or more positive prick tests to common inhalant allergens and/or a positive Phadiatop test. Sensitivity to MR was defined by either one or more positive skin-prick tests to a MR either by the presence of specific IgE.

The study was approved by the Ethics Committee and subjects signed an informed consent to participate in the study.

The statistical analyses included chi-square tests to compare percentages and unpaired *t*-tests to compare mean values of continuous variables. In all instances, a *P*-value less than 0.05 was considered as significant.

Results

Seven hundred and forty-seven subjects were included in the study but only 258 completed the study. Answers to the questionnaire from the 489 subjects who did not undergo skin-prick tests and blood sampling were analysed to evaluate the percentage of atopic patients in this group. Among the 489 subjects who did not participate in the study, 167 (34%) were atopic according to the questionnaire, i.e. a similar rate (33%) to the 258 tested subjects. Age and sex distribution were similar in those who participated and in those who did not.

The proportion of subjects who had a history of previous GA and the mean number of these GA were similar in the 489 subjects who did not participate in the study and the 258 tested subjects.

Among these 258 subjects (Table 1) mean ($\pm$ SD) age was 32.1 ± 5.3 years. Twenty-four of 258 (9.3%) were sensitized to MR: 12 had positive skin-prick tests to one or more MR, and 14 had specific IgE to quaternary ammonium ions. Two had both positive tests.

Among the 12 positive skin-prick tests to MR, three were positive to vecuronium, five to pancuronium, six to suxamethonium and none for atracurium. Two were both positive to suxamethonium and pancuronium. The sex ratio was identical in both the sensitive and non-sensitive groups. Prevalence of atopy defined by the presence of one or more positive prick tests to common inhalant allergens and/or positive Phadiatop test was equal to 16/24 (66.7%) in sensitized subjects, and 121/234 (56%) in non-sensitive subjects and was not significantly different. A history of previous GA was found with the same rate

Table 1. Characteristics of the studied groups

Subjects (<i>n</i>)	258
Males	123
Females	135
Age (years)	32.1 ± 5.3
Atopy (<i>n</i>)	137
Sensitization to MR	24
Positive skin tests	12
Specific IgE	14 (2 with positive skin tests)

in sensitized subjects (16/24; 66.7%) and non-sensitized subjects (168/234; 71.8%). Mean number of previous GA was 2.2 and 2.1, respectively. Reactions during previous GA were only one among MR sensitive and five among non-sensitive subjects. There was no significant statistical difference. A history of drug allergy was found in 42 subjects (Table 2). Among these 42 subjects two were sensitive to MR. This prevalence was not statistically different from the 216 subjects without drug allergy.

Discussion

The prevalence of MR sensitivity in our study was equal to 9.3%. We feel this figure is truly representative of MR sensitivity in this population aged 20–40, since sex, age distribution, proportion of subjects who had previous GA, mean number of previous GA and prevalence of symptoms suggestive of atopy were identical in subjects who agreed to participate in the study and those who did not. The percentage of positive Phadiatop tests was only slightly higher in the study group (26%) than in another sample of the general population studied previously (20%) [8]. Subjects volunteering for a check-up examination in French Social Security health care centres do not differ from the general population with regard to age, sex and education [9] and from those who do not attend, in respect to medical history [10].

Atopy does not appear to be a risk factor for MR allergy. Prevalence of MR sensitivity was not higher in atopic than in non-atopic subjects. In this study, the rate of atopy is high because we considered results of skin tests and results of the Phadiatop test.

When considering atopy only using the Phadiatop test, the rate of atopy was 6/24 (25%) in MR-sensitized subjects and 2/234 (26%) in the non-sensitive subjects. When considering atopy only using skin-prick tests to common

inhalant allergens, we found a rate of atopy of 13/24 (54%) and 90/234 (38%) in MR-sensitive subjects and non-sensitive subjects, respectively. These results are not statistically different.

Equally, the number of previous GA was not different between sensitive and non-sensitive subjects. In our study, drug allergy isolated from or associated with atopy does not represent a risk factor for MR sensitivity. However, in another study, subjects with atopy and drug allergy were sensitized to MR in 16% of cases whereas subjects without these risk factors were sensitive in only 1.6% of cases [4]. A recent study [11] evaluated the rate of sensitivity to MR in selected subjects referred to an allergy division for allergy investigation. They were split into several groups depending on the presence of potential risk factors as atopy, previous occupational exposure to MR, previous GA with MR and previous systemic drug reaction.

Atopy alone was not found as an independent risk factor. The rate for MR sensitivity varied from 0 to 14.7%, depending on the presence or absence of one to several of the above-mentioned possible risk factors. The observed female/male sex ratio was closer to 1 than the 3 expected [2]. However, note that female gender was found as a risk factor for patients with allergic reactions and sensitization to MR. In our survey, we detected only subjects with MR sensitivity without any clinical history of MR sensitization. Levels and affinity of the IgE antibodies to MR and risk factors may be different in both populations.

In a previous study [12], women were systematically tested with MR prior to a GA. Six (8.3%) had a positive skin test with MR but only one had a positive test when using intradermal tests instead of the prick test (1.4%). In our study the rate of positive skin-prick tests to MR was 4.6%. Our study exemplified a large discrepancy between the results of skin tests and presence of specific IgE. Only two subjects had positive skin tests and specific IgE.

Several explanations can be given about the discrepancy between skin test results and biological results. Since the study was performed in a non-selected population, it is possible that some subjects (all tested with the highest concentrations of MR not giving false positive reactions by a non-specific histamine release effect) have a very low sensitivity. In this case, positive skin tests without detectable specific IgE in the sera could be found. The possibility of false positive skin tests can also be kept in mind. However, the concentrations of muscle relaxants were chosen to not induce non-specific histamine release. However, the opposite can also be observed. Some subjects with IgE against quaternary ammonium ions may have positive RAST and negative skin tests, especially for muscle relaxants with rigid structures such as pancuronium or vecuronium [2,13]. In the article describing the PAPPC RIA method [6] used in our work, the sensitivity specificity

Table 2. Characteristics of MR sensitized and non-sensitized subjects. Sensitization was defined as a positive skin test or presence of specific IgE to MR

	Sensitized to MR			Non-sensitized to MR	
	<i>n</i> = 24	(%)		<i>n</i> = 224	(%)
Atopy (<i>n</i>)	16	(67)	NS	121	(56)
Previous GA (<i>n</i>)	16	(67)	NS	168	(72)
Previous GA/subjects	2.2		NS	2.1	
Reactions during GA (<i>n</i>)	1		NS	5	
Drug allergy (<i>n</i>)	2	(8)	NS	40	(17)

GA = general anaesthesia.

and positive predictive value have been evaluated at 97, 97 and 94%, respectively, when studying patients with a history of allergic reaction. However, in the 34 'non-allergic control subjects' tested, two sera with serum-specific IgE antibodies to quaternary ammonium ions were found [6%]. This rate is comparable with the rate of positive sera found in our study (14/258; 5%).

A final and very important practical issue is to determine whether MR allergy is common enough to warrant systematic preoperative screening. No data are available on the general population. In order to be efficient a test must have both a high positive and a high negative predictive value. For a high predictive value the prevalence of the disease in the population must be high. The rate of sensitivity to MR is very high compared with the rate of peroperative anaphylactic reactions to MR. Anaphylactic peroperative reactions occur in around 1/4500 anaesthesias. MR are involved in 59% of cases in adults, i.e. 1/7627 anaesthesias. Thus 1/7627, i.e. 0.013%, have sensitivity which could lead to a peroperative positive reaction. Since 9.3% of the population may have MR sensitivity, 715 preoperative screening tests would have to be performed to identify a patient who could develop a peroperative anaphylactic reaction. The remaining 714 tests could be classified as false positive.

Thus we need to know much more about risk factors for MR allergy before advising a systematic preoperative screening.

In conclusion, at the concentrations used, skin-prick tests to MR and measurement of specific IgE showed a rate of MR sensitivity of 9.3% in a general population. No risk factor for MR sensitivity was identified. Since the rate of peroperative reaction to MR is very low compared with the prevalence of MR sensitivity, a screening test for MR sensitivity prior surgery is not advisable.

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