

Contact sensitization to quaternium-15 acting as a warning sign for curare allergy

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Curare-like compounds are quaternary ammonium salts used as neuromuscular blocking agents (NMBAs) in general anaesthesia. They are responsible for 62% of anaphylactic reactions occurring during anaesthesia, with natural rubber latex proteins being the next most likely cause (1, 2). The chemical structure (3) of curare is critical. The published data show that the presence of two or three quaternary ammonium compounds on the cell surface causes the bridging of immunoglobulin E (IgE) receptor sites on mast cells. This results in massive release of histamine, even with low levels of circulating IgE (Fig. 1). IgE-mediated anaphylactic reactions upon first contact with a muscle relaxant have been reported in 19% (4, 5) to 85% of patients. This suggests a cross-reactive epitope involving a quaternary ammonium group, which can be found in many environmental agents (3). Quaternium-15 is a common contact allergen included in the European baseline series. The prevalence of contact sensitization is as low as 1.2–1.6%, but could represent the first event leading to systemic anaphylactic reaction through a switch from type IV to type I allergy. The aim of our study was to evaluate prospectively, over 3 months, patients with positive quaternium-15 patch test reactions, in order to determine whether they could represent a possible warning sign for the presence of specific anti-NMBA IgE.

Methods and Results

Over a period of 3 months, 6 patients had positive patch test reactions to quaternium-15 among the patient population consulting in our allergology department (1% of 580 patients). They were tested with the allergens of the European baseline series, which contains quaternium-15

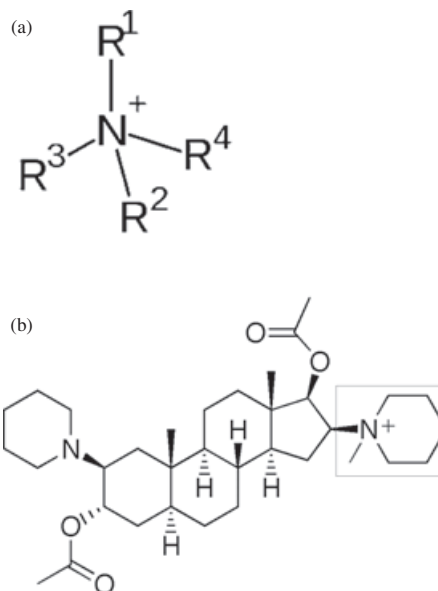


Fig. 1. (a) Chemical structure of quaternary ammonium. (b) Chemical structure of vecuronium. Note the quaternary ammonium group.

1% pet. (Trolab, Almirall-Hermal). Patches were placed on the back with Finn Chambers®, and read by experienced staff on days 2 and 3. Cutaneous reactions were scored from + to +++, according to the International Contact Dermatitis Research Group criteria (6). Blood tests for specific anti-quaternary ammonium and anti-NMBA IgE (radioallergosorbent test) were performed for each patient who had a positive patch test reaction (n = 6). Quantitative results are presented in Table 1. A first control series was obtained from 5 atopic patients without positive quaternium-15 patch test reactions (group 2), and a second control series was obtained from 8 non-atopic patients (group 3) referred for assessment of possible reactions to radiological contrast products. Results are expressed as the percentage of inhibition for the tested allergen in the serum of each patient. A percentage over

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Conflicts of interest: The authors have declared no conflicts.

Table 1. Patient results in groups 1–3

	Age (years)	Sex	Atopic history	Patch test	Anti-quaternary ammonium IgE	anti-NMBA IgE to:			
				Quaternium-15		Suxamethonium	Atracurium	Vecuronium	Pancuronium
Group 1									
1	65	F	Yes	++	12.9	45.34	57.98	62.41	67.01
2	60	F	Yes	+	1.71	–	30.91	–	25.85
3	32	F	Yes	+++	2.42	–	–	24.98	20.65
4	90	F	No	+++	2.82	32.99	42.41	38.21	–
5	49	M	Yes	+	2.61	–	18.15	25.85	–
6	52	F	No	+	13.64	50.53	29.46	46.15	20.72
Group 2									
1	27	M	Yes	–	2.04	—	—	—	—
2	43	M	Yes	–	0.13	—	—	—	—
3	49	M	Yes	–	1.78	—	—	—	—
4	37	M	Yes	–	2.35	—	—	—	—
5	60	M	Yes	–	6.63	—	—	—	—
Group 3									
1	80	F	No	–	<0.1	—	—	—	—
2	64	M	No	–	<0.1	—	—	—	—
3	72	F	No	–	<0.1	—	—	—	—
4	54	M	No	–	<0.1	—	—	—	—
5	61	M	No	–	1.69	—	—	—	—
6	59	M	No	–	1.9	—	—	—	—
7	70	F	No	–	0.91	—	—	—	—
8	59	M	No	–	0.74	—	—	—	—

F, female; M, male.

Results of IgE are given as percentage inhibition.

2% is significant for anti-quaternary ammonium IgE. For NMBA, the percentage of inhibition must exceed 15% to be considered positive.

Discussion

Our study highlights a possible association between positive quaternium-15 patch test reactions and the presence of specific anti-quaternary ammonium and anti-NMBA IgE in the serum.

Positive patch test reactions suggest that contact sensitization from environmental allergens could play a role in this association (3). Quaternium-15 is a formaldehyde releaser that seems to be directly responsible for causing contact dermatitis (7); this may be associated with formaldehyde sensitization. In former studies, more than 50% of patients showed co-sensitization (8, 9). However, none of our 6 patients had a positive formaldehyde patch test reaction, suggesting that, for these patients, allergenicity was not attributable to formaldehyde release.

In our opinion, the hypothesis that cosmetics or cleaning products may induce a first contact sensitization deserves consideration. Indeed, the prevalence of curare anaphylaxis among women is two to six times greater than for men, possibly because of greater environmental

exposure (10). The significance of a positive blood test result for quaternary ammonium seems to be critical, as many atopic patients from our control group had anti-quaternary ammonium IgE. This correlates with the results of Baldo et al. (10), who showed that presence of IgE antibody to morphine, pholcodine and, by extension, to NMBA, must be interpreted according to total IgE antibody level. The correlation between type IV allergic manifestations, serum anti-NMBA IgE and anti-quaternary ammonium IgE in our 6 patients may be explained by this association. The hypothesis of a switch from delayed to immediate hypersensitivity can be postulated, and such associations have already been described. Guillet et al. (11) showed that 37% children followed for natural rubber latex delayed hypersensitivity developed symptoms of type I allergy. In the same way, type I and type IV allergies were associated in 2 of 23 patients presenting both eczema and specific IgE to formaldehyde (6). Moreover, quaternary ammonium compounds are skin irritants, and may also induce the synthesis of IgE by facilitating the spread of allergens through the skin. For 1 of our patients, prick testing showed a perfect correlation between positive prick test reactions and specific serum IgE, signalling a potential warning sign for future anaesthesia.

The main limit of this study is the absence of clinical relevance. None of our patients suffered from previous anaesthetic anaphylaxis, and precise data on their

surgical history were not collected. This should be the aim of future clinical investigations.

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