Acknowledgements

We pay tribute to the chief librarian of E-Da Hospital, Su-Ying Chiu, for professional assistance in retrieving the full text of the eligible articles for literature appraisal and also confirming the completeness of our search.

Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.10.005.

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doi: 10.1016/j.bja.2020.10.005
Advance Access Publication Date: 31 October 2020

Immunoglobulin E cross-linking or MRGPRX2 activation: clinical insights from rocuronium hypersensitivity

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Keywords: allergy; hypersensitivity; immunoglobulin E; mast cell; MRGPRX2; rocuronium; skin test

Editor—Mast cell activation via the MRGPRX2 receptor provides a novel paradigm in our knowledge of immunoglobulin E (IgE)/high-affinity IgE receptor (FcεRI)-independent immediate drug hypersensitivity reactions (IDHRs). However, current evidence for activation of the MRGPRX2 receptor comes from animal or *in vitro* studies, and translation of these findings into clinical relevance in humans is difficult and should be critically interpreted.[1–5]

Based on current models, the MRGPRX2-activating potency of neuromuscular blocking agents (NMBAs) is different and does not correspond to their potency to activate the mouse orthologue. For example, rocuronium is ~12 times less potent at the MRGPRX2 receptor in humans than in mice.[1,3] Consequently, many questions remain unanswered, and speculation and controversy, including suggestions to reclassify hypersensitivity reactions to NMBAs, are emerging.[6,7] However, we think that such a generalised mechanistic reclassification with focus on MRGPRX2 activation is premature and likely unjustified. Specifically, it could entail a significant risk for patients, as it has been suggested that in MRGPRX2-dependent reactions, one could consider re-administration with reduced speed or lower dose.[7]

In an attempt to better understand IgE/FcεRI- and MRGPRX2-dependent mast cell degranulation in response to rocuronium, we retrospectively analysed data from 61 patients from our previously published study on rocuronium anaphylaxis.[8] All 61 patients were investigated between 2 weeks and 24 months after their index reaction, and had a positive skin test for rocuronium (Esmeron®; Merck Sharp & Dohme, Brussels, Belgium). Skin tests included skin prick tests and, if negative, intradermal tests. The maximal test concentration was 10 mg ml^{-1} (undiluted) for skin prick tests and 0.05 mg ml^{-1} (1:200 dilution) for intradermal tests, with dilutions prepared immediately before use. Skin prick tests with a wheal ≥3 mm with surrounding erythema after 15 min were considered positive. For intradermal tests, reactions were read after 20–30 min. Intradermal test responses with a wheal and flare ≥8 mm (or doubling of injection bleb) were considered positive. Negative control (saline buffer) and positive control (histamine 10 mg ml^{-1}; HAL Allergy Benelux NV, Haarlem, the Netherlands) were also tested. Patients were offered subsequent skin tests with succinylcholine, atracurium, and cisatracurium to determine cross-reactivity and safe alternatives. The basophil activation test (BAT) for rocuronium was performed, as described.[8] Results were expressed as the net percentage of $CD63^{+ve}$ basophils, and threshold of positivity was set at 4%. Total IgE and specific IgE to morphine were quantified by the ImmunoCAP system (Phadia Thermo Fisher, Uppsala, Sweden) according to the manufacturer's instructions. For morphine, the decision threshold was set at 0.35 kUA L^{-1}.[9]

As shown in Table 1, when these rocuronium-hypersensitive patients were stratified *post hoc* as patients with positive or negative *in vitro/ex vivo* tests, we observed different skin testing patterns. In patients with a combined positive IgE to morphine and rocuronium BAT suggestive of an IgE/FcεRI-dependent mechanism, skin mast cells appeared to be more sensitive, and skin tests were generally positive in skin prick tests or intradermal test dilutions beyond the concentrations required to trigger non-specific skin test responses (χ^2: skin prick test positivity 30/36 [83%] *vs* 12/25 [48%]; P=0.003). In patients with negative sIgE to morphine and negative rocuronium BAT, skin tests were positive in only 12/25 (48%) of patients in skin prick test settings, and for intradermal tests, higher concentrations were required to reach positivity.

We cannot completely exclude negativisation, defined as originally positive tests becoming negative over time, of *in vitro/ex vivo* investigations in some patients. However, given comparable timing of testing in both groups, we speculate that skin test responses in the 41% of patients with negative sIgE and BAT results were caused by activation of MRGPRX2 receptors on skin mast cells.[8] 'Cross-reactivity' to the benzylisoquinolines atracurium and cisatracurium was rare in both groups. Although additional skin tests with succinylcholine were positive in 9/36 patients with *in vitro/ex vivo* evidence for IgE/FcεRI-mediated rocuronium hypersensitivity and 3/24 patients with negative *in vitro/ex vivo* results, there was no significant difference. However, succinylcholine appears not to be an agonist for MRGPRX2, so it would be interesting to compare the predictive value of the outcome of skin tests with this NMBA in larger groups of patients with positive and negative *in vitro/ex vivo* tests.[1]

Other than biochemical evidence of mast cell activation[10] being more frequent in the group with a presumed IgE reaction, no other differences with respect to tryptase were demonstrable. Most importantly, acute and delta tryptase level was not indicative of the mechanistic process. Finally, we show total IgE to be higher in the group with positive skin tests

Table 1 Characteristics and laboratory findings of patients with positive skin tests to rocuronium. BAT, basophil activation test; IgE, immunoglobulin E; NAP6, National Audit Project 6; NS, not significant; sIgE, specific IgE. BAT results are expressed as net percentages $CD63^{+ve}$ cells. Note that sIgE to morphine is used as biomarker for sensitisation to substituted ammonium structures[7] For skin test procedures, see Spoerl and colleagues.[6] *Acute minus baseline tryptase. †Mast cell activation was defined by an acute tryptase equalling or exceeding 1.2×baseline+2 μg L^{-1}.[8] For the group with a presumed IgE reaction, NAP6 score was unclear in two patients; for the other group with negative sIgE and BAT, NAP6 score is unknown in one patient. Baseline tryptase was not determined in eight presumed IgE and two possible MRGPRX2 patients, respectively. Total IgE values were unknown in four and one patients, respectively.

Parameter	Positive sIgE and BAT (most likely IgE)	Negative sIgE and BAT (possibly MRGPRX2)	*P* Value
Number (%)	36 (59)	25 (41)	
Male/female, *n*	10/26	10/15	NS
Age (yr), median (range)	52 (17–75)	56 (15–75)	NS
NAP6 1/2/3/4 score	1/1/23/11	4/3/14/3	NS
Interval index reaction: testing (days), median (range)	70 (15–624)	109 (37–542)	NS
Baseline tryptase (μg L^{-1}), median (range)	4.9 (1.3–16.7)	5.3 (1.8–14)	NS
Acute tryptase (μg L^{-1}), median (range)	17.9 (8.8–200)	19.9 (3.6–175)	NS
Delta tryptase (μg L^{-1}), median (range)*	40.6 (7.5–194.7)	15.1 (−0.8 to 169.6)	NS
Mast cell activation (yes/no)†	22/0	10/5	0.004
Total IgE (kU L^{-1}), median (range)	174 (18–22 450)	64 (11–487)	0.006
SIgE morphine (kUA L^{-1}), median (range)	3.13 (0.4–100)	0.05 (0.05–0.31)	/
BAT: $\%CD63^{+ve}$ cells, median (range)	28 (5–90)	/	/
Rocuronium-positive SPT, *n* (%)	30 (83)	12 (48)	0.002
Rocuronium-positive IDT at 0.05 mg ml^{-1} only, *n* (%; highest concentration)	1 (0.03)	9 (36)	0.024
Positive skin test for			
Succinylcholine	9/36	3/24	NS
Atracurium	2/35	4/22	NS
Cisatracurium	5/36	4/21	NS

and *in vitro/ex vivo* tests. Together with the sometimes highly elevated titres and persistence of positive tests for up to 2 yr, we think these findings likely reflect an IgE rebound phenomenon because of intercurrent use of pholcodine-containing antitussives, which is known to be associated with elevated total IgE.[9]

Evidence is emerging that occupancy of MRGPRX2 receptors could constitute a novel endotype of IDHRs, including anaphylaxis from NMBAs. Here, we show that a generic mechanistic reclassification may be incorrect. In the majority of patients, the diagnosis of an IgE-mediated reaction to rocuronium is established by a combination of skin tests and *in vitro/ex vivo* tests. To the best of our knowledge, this is the first attempt to explore clinical and biological features in IgE-dependent and likely MRGPRX2-dependent rocuronium anaphylaxis. If our classification is correct, it seems that clinical details, acute tryptase, and delta tryptase are indistinguishable. In contrast, skin mast cells that strongly express MRGPRX2[11] appear to be less sensitive in the MRGPRX2-dependent group. In the absence of a reference test to document MRGPRX2-dependent anaphylaxis, and because of the longer interval between index reaction and testing, it cannot be excluded that some patients with negative *in vitro/ex vivo* tests (the possible MRGPRX2 group) have in fact experienced an IgE-dependent reaction. Thus, we firmly discourage any re-administration of NMBAs in skin-test-positive patients, irrespective of the results of *in vitro/ex vivo* tests.

Funding

Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (1800614N) to DGE, (1113617N) to ALVG, (1804518N) to VS, (G069019N).

Declarations of interest

The authors declare that they have no conflicts of interest.

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doi: 10.1016/j.bja.2020.10.006
Advance Access Publication Date: 3 November 2020

Factors affecting need for manipulation after total knee arthroplasty: a retrospective case–control cohort study

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