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Association between mutated Mas-related G protein-coupled receptor-X2 and rocuronium-induced intraoperative anaphylaxis. Comment on *Br J Anaesth* 2020; 125: e446–e448

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Keywords: immediate drug hypersensitivity; MRGPRX2; neuromuscular blocking agent; perioperative anaphylaxis; rocuronium

Editor—We read with great interest the paper by Suzuki and colleagues[1] about the association between the Mas-related G protein-coupled receptor-X2 (MRGPRX2) and rocuronium-induced perioperative anaphylaxis. The authors describe a patient who experienced severe perioperative anaphylaxis. Based on a positive intradermal skin test (IDT) and a negative serum-specific IgE (sIgE) antibody result to rocuronium, the authors posit this reaction to have resulted from occupation of MRGPRX2 by the aminosteroid-derived neuromuscular blocking agent (NMBA) rocuronium. However, we would like to express some comments and concerns about their diagnosis and interpretation of the data. Perioperative anaphylaxis constitutes a significant condition with serious consequences of diagnostic mismanagement.[2] In this respect, firstly establishing the correct cause of the reaction and secondly resolving between IgE- and MRGPRX2-dependent reactions are critical for NMBA stewardship.

In this case, the diagnosis of rocuronium hypersensitivity relied upon a positive IDT with undiluted rocuronium (10 mg ml^{-1}) without details about injection volume, injection bleb, or final wheal and flare reaction. Most importantly, the test concentration is 200-fold the maximum non-irritative concentration of 0.05 mg ml^{-1} as recommended for IDT in the recent *European Academy of Allergy and Clinical Immunology* position paper on the investigation of perioperative immediate hypersensitivity reactions.[3] Therefore, a false-positive result of IDT cannot be excluded, as this concentration is likely to induce wheal and flare responses in healthy control individuals.[4]

Moreover, it seems that not all compounds that the patient was exposed to were tested (e.g. remifentanil); other important compounds (e.g. latex and chlorhexidine) were simply not investigated, and for lidocaine and cefazolin, investigations should have included a challenge test.[5] Furthermore, a negative rocuronium sIgE result does not rule out an IgE-mediated rocuronium allergy. We have shown the negative predictive value for sIgE rocuronium to be 72%, compared with 95% for skin testing and 75% for basophil activation testing (BAT).[6] Therefore, the basis for confirming rocuronium as cause is inadequate, and the anaphylaxis in this patient may have resulted from another cause.

We also respectfully disagree with the statement that the negative rocuronium sIgE result excludes cross-reactivity with vecuronium, another aminosteroid-derived NMBA that was used earlier in this patient. A morphine-based sIgE assay could have been a more sensitive method to detect an eventual sensitisation to substituted tertiary and quaternary ammonium structures, the major antigenic determinant of NMBAs.[7,8] Moreover, potential cross sensitisation could have been explored by skin testing or BAT, as the latter more closely mirrors the *in vivo* situation than traditional sIgE binding assays,[6,9–11] as described in a recent review on the value and

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limitations of BAT in perioperative hypersensitivity and anaphylaxis.[12]

This case report does offer an opportunity to consider the molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis, as recently reviewed.[13] Mast cell degranulation via off-target occupation of the MRGPRX2 heralds a new domain in our knowledge of immediate drug hypersensitivity,[14] and challenges the dogma that NMBAs mainly cause IgE-dependent anaphylaxis that can be documented by positive skin testing believed to be specific for an IgE-mediated mechanism.[15] However, based on the limited evidence currently available in the literature, we think that it is incorrect and potentially dangerous to reclassify the majority of rocuronium-related anaphylaxis as MRGPRX2-dependent reactions, which have been speculated to be preventable by reducing the speed of administration or lowering the dose.[15] In our experience, the majority of patients with skin-test-proved rocuronium anaphylaxis have their diagnosis further confirmed by sIgE serology and BAT.[6,16] Furthermore, there is currently no evidence for non-specific triggering by rocuronium of basophil or mast cell degranulation in humans via wild-type MRGPRX2.[17,18] Clearly, such patients should be warned against this NMBA until thoroughly investigated, including testing with other NMBAs to identify safe alternatives for the future.

Finally, it is of note that the authors emphasise the expression of MRGPRX2 by basophils, as claimed by Wedi and colleagues,[19] and the role these cells play in IgE-independent perioperative anaphylaxis in humans. However, we would like to point out that there is little, if any, irrefutable evidence for IgE-independent basophil degranulation in response to anaesthetics and related compounds, and that constitutive expression of MRGPRX2 by basophils is a subject of ongoing controversy. First, *ex vivo* basophil activation experiments for perioperative anaphylaxis have mainly been validated in the context of allergy to beta-lactam antibiotics (e.g. aminopenicillins and cefazolin), natural rubber latex (from *Hevea brasiliensis*), and chlorhexidine, all IgE-mediated conditions par excellence.[12] With respect to NMBAs, such as rocuronium, succinylcholine, and atracurium, in a large majority of our patients with positive BAT results, concomitant positive skin testing and sIgE results generally point to an IgE-dependent mechanism.[6,8,10,11,16] Note that a specific IgE:total IgE ratio does not benefit diagnosis of rocuronium allergy.[20] Second, the statement that basophils constitutively express MRGPRX2 is difficult to align with the negative results observed in control individuals enrolled in several studies on BAT with potent MRGPRX2 agonists, such as opiates, vancomycin, and fluoroquinolones that are well known to elicit non-specific histamine release by skin mast cells.[21–25]

Mast cell degranulation via off-target occupation of the MRGPRX2 heralds a new domain in our knowledge of immediate drug hypersensitivity. However, in most patients who experience rocuronium anaphylaxis, a positive IDT to rocuronium, using non-irritative test concentrations, is likely to reflect IgE-dependent sensitisation that should be explored by quantification of sIgE and BAT with identification of safe alternatives for the future. In more rare cases, displaying negative sIgE and BAT results, genetic analyses to identify pathogenic MRGPRX2 polymorphisms/mutations could help to further elucidate the conundrum of MRGPRX2-related anaphylaxis and identify patients at risk to other agonists of the MRGPRX2. Before conclusions can be formulated about underlying mechanisms of perioperative anaphylaxis, diagnostic work-up should be carried out in a standardised way and according to the guidelines.

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Declarations of interest

The authors declare that they have no conflict of interest.

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Measurement of pholcodine-specific IgE in addition to morphine-specific IgE improves investigation of neuromuscular blocking agent anaphylaxis

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Keywords: allergy; anaphylaxis; hypersensitivity; morphine; neuromuscular blocking agent; perioperative; pholcodine; specific IgE

Editor—Neuromuscular blocking agents (NMBAs) are one of the leading causes of perioperative hypersensitivity reactions.[1,2] Investigation of these reactions typically includes skin testing and measurement of specific immunoglobulin E (sIgE) where available. Different patterns of NMBA cross-reactivity between patients appear to indicate variability in the IgE binding epitopes recognised.[3] Specific IgE to NMBAs is frequently examined using morphine as a marker for the substituted ammonium groups considered to be the main allergenic epitopes of NMBAs.[4] Pholcodine is a morphine derivative that has also been suggested as an effective marker for detection of sIgE to substituted ammonium epitopes.[5] However, considerable variation can be seen between sIgE concentrations to morphine or pholcodine in NMBA-allergic patients. The analysis reported here was undertaken to investigate these variations and the value of the pholcodine-sIgE assay in the assessment of NMBA-allergic patients.

A retrospective study was carried out for all patients investigated at the Royal North Shore Hospital Anaesthetic Allergy Clinic (Sydney, Australia) from June 2009 to September 2019. Standardised skin testing was performed according to protocols outlined by the Australian and New Zealand Anaesthetic Allergy Group[6] with a panel of NMBAs including rocuronium, vecuronium, pancuronium, succinylcholine, and cisatracurium. Measurement of pholcodine and morphine sIgE