BJA

British Journal of Anaesthesia, 125 (6): e443–e474 (2020)

CORRESPONDENCE

Application of specific-to-total IgE ratio does not benefit diagnostic performance of serologic testing for rocuronium allergy

Marie-Line M. Van Der Poorten[1,2], Gustavo Molina-Molina[3], Athina L. Van Gasse[1,2], Margo M. Hagendorens[1,2], Margaretha A. Faber[1], Leander De Puysseleyr[1], Jessy Elst[1], Christel M. Mertens[1], Tatsuo Horiuchi[4], Vito Sabato[1] and Didier G. Ebo[1,*]

[1]Faculty of Medicine and Health Sciences, Department of Immunology, Allergology, Rheumatology and Infla-Med Centre of Excellence, Antwerp, Belgium, [2]Faculty of Medicine and Health Sciences, Department of Paediatrics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium, [3]Department of Allergology, Vall D'Hebron University Hospital, Barcelona, Spain and [4]Department of Anaesthesiology, Gunma University Graduate School of Medicine, Gunma University Hospital, Maebashi, Gunma, Japan

*Corresponding author. E-mail: immuno@uantwerpen.be

Keywords: allergy; hypersensitivity; IgE; morphine; perioperative; pholcodine; rocuronium

Editor—The diagnostic approach of a suspected immediate perioperative allergic reaction, generally starts with skin testing and quantification of drug-reactive specific IgE (sIgE) antibodies. As recently addressed in this journal,[1] suspected immediate perioperative allergic reactions are rare but potentially life-threatening. For example in our recent series,[2] 400 of 608 patients had a grade 3 or 4 reaction according to the 6th National Audit Project (NAP6) classification.[3] Unfortunately, correct diagnosis of suspected immediate perioperative allergic reactions can be challenging. The standard reference test for accurate diagnosis of suspected immediate perioperative allergic reactions is a controlled drug challenge. Because of obvious ethical and practical limitations, drug challenges are mainly advocated in difficult cases with equivocal or negative results. Therefore, in clinical practice, the diagnostic approach of suspected immediate perioperative allergic reactions generally starts with skin testing and quantification of sIgE antibodies.[4] Unfortunately, measurement of serum sIgE is highly variable and therefore often unreliable, especially for β-lactam antibiotics and neuromuscular blocking agents.[5]

Correct serologic diagnosis of rocuronium allergy is hampered by clinically irrelevant positive sIgE results because of non-specific binding to the solid phase, for example in cases of high serum total IgE (tIgE).[6] We suggest that calculation of a drug-specific ratio could help clarify the interference of tIgE on sIgE results and increase specificity of the assay. It has been shown that this strategy might be helpful in optimising serologic diagnosis of allergy to β-lactam antibiotics including cefazolin.[7] However, no data regarding the application of the sIgE/tIgE ratio in other drug allergies are available. This study aims at exploring the value of a sIgE/tIgE ratio in the diagnosis of rocuronium allergy, a major cause of perioperative anaphylaxis.[2]

The local ethics committee approved this retrospective observational study (reference number B300201316408), and patients or their representatives approved an informed consent in accordance with the Declaration of Helsinki. Patients and exposed control individuals were included by trained physicians from the outpatient clinic of allergology of the Antwerp University hospital between 2002 and 2018. A total of 55 rocuronium allergic patients (ROCU+) who were referred because of a suspected perioperative hypersensitivity reaction were selected. Of these, 53 experienced a grade 3 or 4 reaction. Diagnosis of rocuronium allergy was based on a positive skin test and basophil activation test (BAT). In all patients, sIgE to rocuronium was available. Respectively, 53 ROCU+ sIgE to morphine and pholcodine and 23 biomarkers of sensitisation to tertiary and quaternary substituted ammonium structures were also available. An exposed control group (n=130) was included comprising individuals with a negative skin test and BAT for rocuronium (ROCU−). In these ROCU− patients, an alternative cause for their suspected perioperative hypersensitivity was found. In 61, 124, and 27 patients a sIgE result for rocuronium, morphine, or pholcodine, respectively, was available.

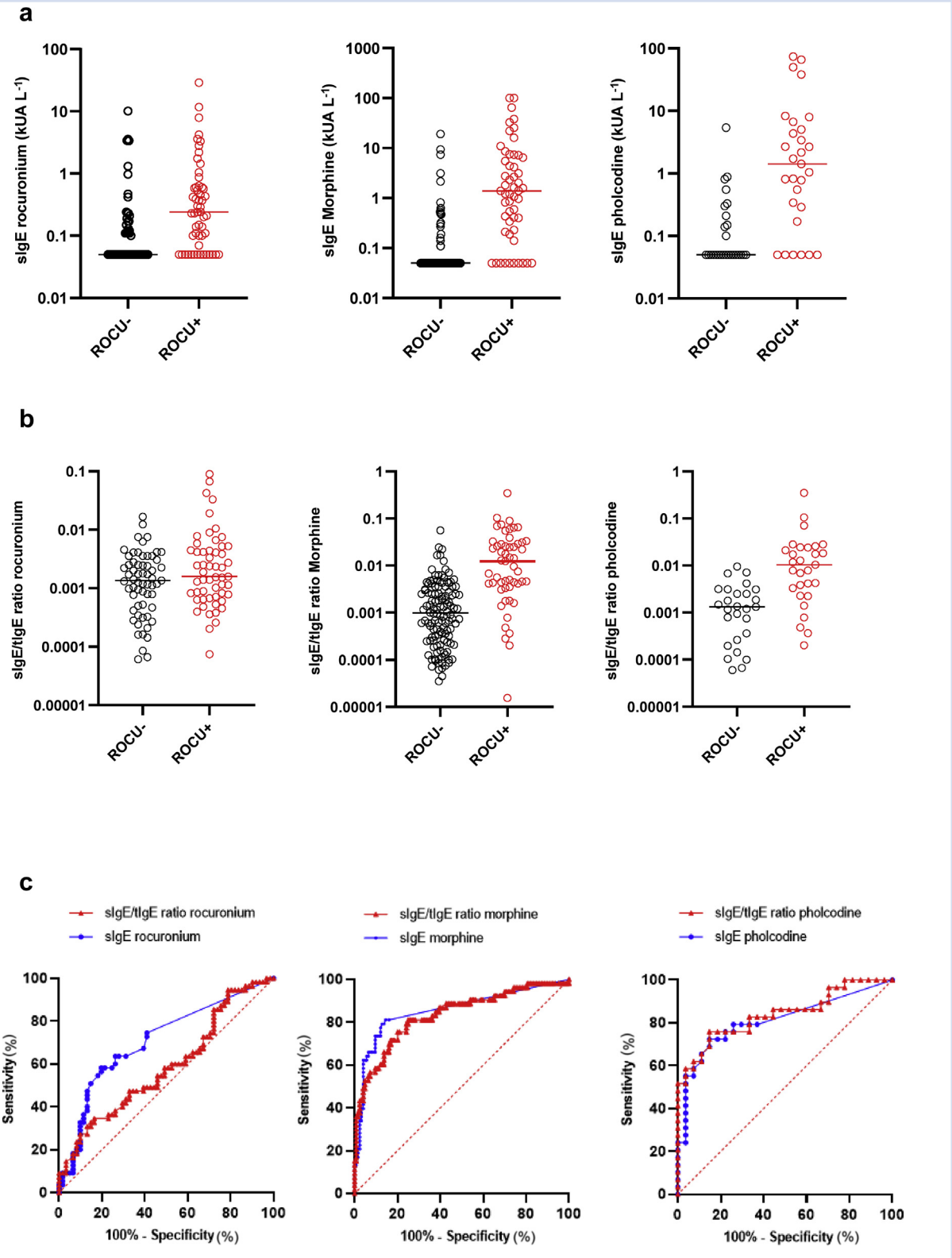

Fig 1. (a) Specific IgE (sIgE) values to rocuronium, morphine and pholcodine in exposed control individuals (black circles) and patients exhibiting perioperative hypersensitivity (red circles). A horizontal line is showed at the median. Values below the detection limit were set at 0.05 kUA L^{-1}. (b) sIgE/tIgE ratio values in patients and controls. A horizontal line is shown at the median. (c) Receiver operating characteristic curves for specific IgE quantification (blue circles) and sIgE/tIgE ratio calculation (red triangles) for rocuronium, morphine, and pholcodine.

Skin tests and BAT for rocuronium were performed as described.[8] Total and specific IgE to rocuronium, morphine, and pholcodine were quantified with an ImmunoCAP technique (Thermo-Fisher, Uppsala, Sweden) with a technical detection limit of 0.10 kUA L^{-1}.[6] Drug-specific decision thresholds for morphine and pholcodine were set at 0.35 kUA L^{-1}, and for rocuronium at 0.13 kUA L^{-1} as validated elsewhere.[6] sIgE values <0.10 kUA L^{-1} were arbitrarily set at 0.05 kUA L^{-1}. sIgE/tIgE ratios were calculated by dividing the sIgE result by total IgE. Receiver operating characteristic curves were used to compare the diagnostic performance of sIgE quantification with calculation of the sIgE/tIgE ratio.

We included a total of 55 ROCU+ patients. Supplementary Table S1 shows the characteristics of participants. The time elapsed between reaction and testing was known in 52/55 patients of whom rocuronium sIgE was determined, with a median of 2 months (range 1–59). The time between reaction and testing was known in 50/53 morphine patients and 28/29 pholcodine patients, with a median of 2 months (range 1–59) and 2.5 months (range 1–10), respectively. In ROCU+ and ROCU− groups, mean total IgE values were not increased. In ROCU+ patients, the median sIgE for rocuronium, morphine, and pholcodine was significantly higher than for ROCU− patients ($P<0.001$, Mann–Whitney *U*-test) (Fig. 1a). For ROCU+ patients, the median (range) for tIgE was 126 (56–340) kUA L^{-1} and was not significantly different from that of ROCU− patients, 56 (26–343.5) kUA L^{-1} ($P=0.10$, Mann–Whitney *U*-test). The median of sIgE/tIgE ratios for morphine and pholcodine were significantly higher in ROCU+ as compared with ROCU− patients (Fig. 1b; $P<0.001$, Mann–Whitney *U*-test). This was not the case for sIgE/tIgE rocuronium ($P=0.1039$, Mann–Whitney *U*-test). We analyzed the sensitivity and specificity of the different diagnostic methods using receiver operating curves (Fig. 1c).

Our analyses showed that quantification of sIgE values to rocuronium (area under the curve [AUC]=0.7) performed significantly better than the sIgE/tIgE ratio (AUC=0.59, $P=0.041$) for differentiating between patients and controls, whereas for morphine and pholcodine no significant difference between AUCs was found. Hence, no calculation of optimal cut-off values for sIgE/tIgE was performed. Exact AUC values and the differences between them are shown in Supplementary Table S2.

Sensitisation to neuromuscular blocking agents is in general assessed serologically using techniques that quantify drug-sIgE antibodies, such as to suxamethonium, rocuronium, and atracurium.[2,5] From earlier studies, sensitivity, specificity, and predictive values for sIgE assays for rocuronium, for a drug-specific threshold of 0.13 kUA L^{-1},[6] vary between 72% and 83%, leaving room for improvement.[9] From our data, it emerges that application of rocuronium sIgE/tIgE ratio does not improve the positive likelihood of the rocuronium sIgE assay, likely because of the mean normal tIgE values in both our ROCU+ and ROCU− groups.

Unlike sensitisation to benzylisoquinoline neuromuscular blocking agents, sensitisation to rocuronium can also be explored indirectly by measuring IgE reactivity to tertiary and quaternary substituted ammonium structures that are considered to be the major epitopes using morphine-based assay, pholcodine assay, or both.[6,9] Unfortunately, sIgE to these opioids is prevalent in the general population, and an isolated positive sIgE result to morphine does not preclude subsequent use of a neuromuscular blocking agent.[10] As for the rocuronium sIgE/tIgE ratio, we observed that the sIgE/tIgE ratio for both opioids did not benefit diagnosis of rocuronium allergy. The reason why these findings do not align with our previous observations[6] is likely that, in contrast to our former study, we did not actively select patients with elevated tIgE titres. The current study was restricted to patients attending because of a suspected perioperative hypersensitivity reaction.

In conclusion, application of specific/total IgE ratios for rocuronium, morphine, and pholcodine does not benefit the positive likelihood and overall diagnostic performance of serologic testing for rocuronium allergy. Quantification of sIgE values to rocuronium performed significantly better than the sIgE/tIgE ratio for differentiating between patients and controls. For morphine and pholcodine, no significant difference between the AUC was found. The reason for this is likely because the mean total IgE values were normal in both ROCU− and ROCU+ groups, whereas increased values could have resulted in non-specific binding to the solid phase as reported.[6] We can conclude that the calculation of a drug-specific sIgE/tIgE ratio for rocuronium, morphine, and pholcodine does not benefit the serologic diagnosis of rocuronium allergy.

Declarations of interest

DGE is a senior clinical researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1800614N). ALVG is a fellow of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1113617N). VS is a senior clinical researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1804518N). Foundation Flanders/Fonds Wetenschappelijk Onderzoek Project (G069019N). GMM is a fellow of the EAACI research fellowship 2020. The authors declare no other conflicts of interest related to this publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.032.

References

1. Garvey LH, Dewachter P, Hepner DL, et al. Management of suspected immediate perioperative allergic reactions: an international overview and consensus recommendations. *Br J Anaesth* 2019; **123**: e50–64
2. Ebo DG, Van Gasse AL, Decuyper II, et al. Acute management, diagnosis, and follow-up of suspected perioperative hypersensitivity reactions in Flanders 2001–2018. *J Allergy Clin Immunol Pract* 2019; **7**: 2194–204. e7
3. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
4. Garvey LH, Ebo DG, Mertes PM, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy* 2019; **74**: 1872–84
5. Takazawa T, Sabato V, Ebo DG. In vitro diagnostic tests for perioperative hypersensitivity, a narrative review: potential, limitations, and perspectives. *Br J Anaesth* 2019; **123**: e117–25

6. Ebo DG, Venemalm L, Bridts CH, et al. Immunoglobulin E antibodies to rocuronium: a new diagnostic tool. *Anesthesiology* 2007; **107**: 253–9
7. Van Gasse AL, Sabato V, Degerbeck F, et al. Specific IgE to cefazolin: does it benefit diagnosis? *J Allergy Clin Immunol Pract* 2019; **7**: 2932–4
8. Ebo DG, Bridts CH, Hagendorens MM, Mertens CH, De Clerck LS, Stevens WJ. Flow-assisted diagnostic management of anaphylaxis from rocuronium bromide. *Allergy* 2006; **61**: 935–9
9. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9
10. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75

doi: 10.1016/j.bja.2020.05.032
Advance Access Publication Date: 30 June 2020

Association between mutated Mas-related G protein-coupled receptor-X2 and rocuronium-induced intraoperative anaphylaxis

Yasuyuki Suzuki[a,*], Shuang Liu[b], Fumito Kadoya[a], Yasushi Takasaki[b], Toshihiro Yorozuya[b] and Masaki Mogi[b]

[a]Matsuyama City, Ehime, Japan and [b]Toon City, Ehime, Japan

*Corresponding author. E-mail: ysuzuki1978@gmail.com

Keywords: allergy testing; anaphylaxis; MRGPRX2; neuromuscular blocking agent; non-IgE-mediated allergic reaction; rocuronium

Editor—Unexpected perioperative anaphylaxis is one of the most challenging clinical scenarios for anaesthesiologists.[1] The perioperative drugs most likely to cause anaphylaxis are antibiotics, neuromuscular blocking agents (NMBAs) and opioids. Recent studies have shown that NMBAs and opioids directly stimulate the Mas-related G protein-coupled receptor b2 (Mrgprb2), which is specifically expressed by mouse mast cells and which induces mast cell histamine release.[2] This immunoglobulin E (IgE)-independent pathway is referred to as a non-IgE-mediated allergic reaction. Some anaphylaxis cases caused by NMBAs have a negative basophil activation test (BAT), an IgE-mediated allergic reaction test, despite having a positive skin test.[3] We postulated that the Mas-related G protein-coupled receptor X2 (*MRGPRX2*), which is the human orthologue of mouse *Mrgprb2* and is expressed in mast cells, peripheral blood basophils, and eosinophils,[4] plays a key role in non-IgE-mediated perioperative anaphylaxis in humans.

We present a case of perioperative anaphylactic reaction to rocuronium, a widely used NMBA. Informed consent was obtained from the patient for the publication of this case report. All research protocols were approved by the Ehime University Committee for clinical research and Saiseikai Matsuyama Hospital Committee for Clinical Research, and registered as UMIN000032695 on UMIN-CTR Clinical Trial. As specific IgE antibodies against rocuronium were not detected, this reaction was diagnosed as a non-IgE-mediated allergic reaction. Furthermore, we identified specific mutations in the *MRGPRX2* DNA sequence likely associated with the development of hypersensitivity to rocuronium.

A 30-yr-old male (59 kg, 173 cm) was scheduled for open reduction and internal fixation of a clavicle fracture under general anaesthesia. He had a history of bullectomy under general anaesthesia 10 years ago with propofol, remifentanil, and vecuronium and cefazoline as a preoperative antibiotic. Upon arrival in the operating room, his arterial BP, HR, and peripheral oxygen saturation (SpO_2) were 120/62 mm Hg, 60 beats min^{-1}, and 100%, respectively. Anaesthesia was induced i.v. with propofol (target-controlled infusion mode at 3.0 μg ml^{-1}), remifentanil 0.25 μg kg^{-1} min^{-1}, lidocaine 50 mg, fentanyl 100 μg, and rocuronium 50 mg. At 2 min after rocuronium infusion, HR increased to 143 beats min^{-1} and subsequently BP decreased to 60/28 mmHg together with appearance of erythema and wheals over his entire body. After tracheal intubation, SpO_2 decreased to 89% with wheezing while receiving mechanical ventilation (fraction of inspired oxygen [FiO2]: 0.4).

Incremental doses of ephedrine (8 mg, three doses) and phenylephrine (0.1 mg, five doses) were administered i.v., but BP and HR failed to respond to these interventions, and SpO_2 did not recover even with inspired oxygen concentration at 100%. Suspecting an anaphylactic reaction to anaesthetic drugs, we stopped the infusion of propofol, and 4 vol% desflurane was administered and methylprednisolone 125 mg i.v. was administered with a continuous infusion of norepinephrine (0.1 μg kg^{-1} min^{-1}), which increased BP to 110/58 mmHg and decreased his HR to 85 beats min^{-1}. Respiratory status

DOI of original article: 10.1016/j.bja.2020.08.035.