

Hypersensitivity to Neuromuscular Blocking Agents: Can Skin Tests Give the Green Light for Re-Exposure?



Vito Sabato, MD, PhD^{a,b}, and Didier G. Ebo, MD, PhD^{a,b} Antwerp, Belgium

Perioperative hypersensitivity (POH) is a rare but potentially life-threatening condition with costly consequences of diagnostic error. All exposures in the perioperative setting may potentially be the cause of a hypersensitivity reaction, but in different countries, neuromuscular blocking agents (NMBA) have traditionally been reported to be implicated most commonly.¹ The definite standard for correct diagnosis of immediate drug hypersensitivity reactions is a controlled drug provocation test (DPT). However, for curarizing NMBA, a full-dose DPT with the culprit and potential safe alternatives for the future are difficult and rarely considered for obvious reasons. Consequently, diagnostic workup of NMBA hypersensitivity generally starts with judicious skin testing (ST)²⁻⁴ eventually complemented with quantification of specific IgE (sIgE) antibodies and/or basophil activation tests (BAT).⁵ This workup should aim at determining the potential causative role of all administered agents and identification of cross-reactive compounds. However, data on the negative predictive value of these tests based on notes from subsequent anesthesia are scarce.^{6,7}

In this issue of *JACI: In Practice*, Dewachter et al⁸ report results of ST, BAT, and sIgE in 31 patients with a strong suspicion of a hypersensitivity reaction to different NMBA. Patients with positive ST were categorized as “Allergy,” that is, IgE-dependent, and those with negative ST responses as “Non Allergy,” that is, IgE-independent. Furthermore, peak and baseline tryptase values were quantified to depict mast cell activation (MCA). The authors conclude that BAT does not replace ST in the assessment of NMBA hypersensitivity. However, as correctly acknowledged, ST do not exhibit an absolute negative predictive value.^{9,10} Therefore, the question remains whether it is absolutely safe to readminister an NMBA that tested negative in ST, that is, “non-allergy” group, particularly in patients who demonstrated MCA irrespective of the

results of BAT. The current study does not solve this issue, as no patients with negative ST but MCA had re-exposure.

We feel that neglecting MCA in ST-negative patients might entail a risk for subsequent reactions, particularly when the time relationship between administration and onset of symptoms is compatible for NMBA hypersensitivity and when no other alternatives are identified. Whether the BAT in those patients could benefit diagnostic management deserves additional investigations involving all grades of severity and magnitudes of MCA. Moreover, it is not excluded that ST-negative patients without MCA might also benefit from additional BAT. Although in the context of NMBA it is difficult to ascertain the clinical significance of a positive BAT, it has been demonstrated that the positive predictive value (PPV) for BAT for NMBA, as for other drugs, generally exceeds 95%^{11,12} and that for β -lactams, positive BAT were observed in ST-negative patients reacting to a drug challenge.¹³ Alternatively, this study⁸ confirms that quantification of drug-sIgE and sIgE to quaternary ammonium structures should not be used in isolation to diagnose NMBA hypersensitivity.⁷

The diagnostic management of NMBA hypersensitivity cannot be considered as complete when it fails to address the potential of cross-reactivity. In line with previous studies,^{6,7} Dewachter et al,⁸ also by reviewing the notes from subsequent anesthesia, show that both ST and BAT perform similarly in demonstrating low cross-reactivity between NMBA from different classes. An exception was one atracurium reactor with a negative ST to rocuronium who had uneventful exposure to rocuronium despite a positive BAT. Obviously, this single discrepancy needs thorough evaluation as ST and BAT for rocuronium have both been demonstrated to display a high but not absolute PPV, exceeding 95%.¹¹ As we believe that it is ethically difficult to justify an administration in patients demonstrating a positive test with such a high PPV, we currently dissuade further administration in patients with discordant ST and BAT results.

Finally, the authors state that nonallergic, that is, IgE-independent, immediate NMBA hypersensitivity is mild. We believe that prudence should be called regarding this statement and that the severity of a POH reaction does not necessarily reflect the cause nor the mechanism. Recently, it has been demonstrated that various drugs, including NMBA, can elicit MCA through off-target occupancy of MRGPRX2^{14,15} with a clinical picture that is indistinguishable from a genuine IgE-dependent effector cell activation.

In summary, for the time being, ST merits the status as the first-line diagnostic test in the evaluation of NMBA hypersensitivity. However, we believe that BAT can benefit diagnosis in difficult cases with negative or equivocal ST, especially when MCA is evidenced. At the moment there are no irrefutable data supporting the readministration of NMBA in patients with

^aDepartment of Immunology, Allergy, Rheumatology, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

^bDepartment of Immunology, Allergy, Rheumatology, Antwerp University Hospital, Antwerp, Belgium

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 7, 2018; accepted for publication February 10, 2018.

Corresponding author: Didier G. Ebo, MD, PhD, Department of Immunology, Allergy, Rheumatology, Faculty of Medicine and Health Sciences, University of Antwerp, Campus Drie Eiken T5.95, Universiteitsplein 1, 2610 Antwerpen, Belgium. E-mail: immuno@uantwerpen.be.

J Allergy Clin Immunol Pract 2018;6:1690-1. 2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2018.02.008>

suggestive clinical history, MCA, and negative ST. More studies with reviews of anesthetic records of subsequent surgical procedures with NMBA administration are mandatory to fill the gap in our current knowledge about the negative predictive value of both ST and BAT.

Acknowledgments

V.S. is a Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1804518N). DGE is a Senior Clinical Researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1800614N).

REFERENCES

1. Mertes PM, Volcheck GW, Garvey LH, Takazawa T, Platt PR, Guttormsen AB, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016;45:758-67.
2. Mertes PM, Malinovsky JM, Jouffroy L, Working Group of the SFAR and SFAAberer W, Terreehorst I, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2011;21:442-53.
3. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-12.
4. Scolaro RJ, Crilly HM, Maycock EJ, McAleer PT, Nicholls KA, Rose MA, et al. Australian and New Zealand Anaesthetic Allergy Group Perioperative Anaphylaxis Investigation Guidelines. *Anaesth Intensive Care* 2017;45:543-55.
5. Ebo DG, Faber M, Elst J, Van Gasse A, Bridts C, Mertens C, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018;6:1176-84.
6. Ramirez LF, Pereira A, Chiriac AM, Bonnet-Boyer MC, Demoly P. Negative predictive value of skin tests to neuromuscular blocking agents. *Allergy* 2012; 67:439-41.
7. Leysen J, Uyttendaele 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.
8. Dewachter P, Cholle-Martin S, Mouton-Faivre C, de Chaisemartin L, Pascale Nicaise-Roland P. Comparison of basophil activation test and skin testing performances 1 in NMBA-allergy. *J Allergy Clin Immunol Pract* 2018;6:1696-704.
9. Fisher MM, Merefild D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. *Br J Anaesth* 1999; 82:770-3.
10. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005;33:816-9.
11. Leysen J, Bridts CH, De Clerck LS, Vercauteren M, Lambert J, Weyler JJ, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011;66:1014-9.
12. Uyttendaele AP, Sabato V, Leysen J, Bridts CH, De Clerck LS, Ebo DG. Flowcytometric diagnosis of atracurium-induced anaphylaxis. *Allergy* 2014;69: 1324-32.
13. Salas M, Fernandez-Santamaria R, Mayorga C, Barrionuevo E, Ariza A, Posadas T, et al. Use of the basophil activation test may reduce the need for drug provocation in amoxicillin-clavulanic allergy. *J Allergy Clin Immunol Pract* 2018;6:1010-8.
14. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015;519:237-41.
15. Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IgE-mediated, pharmacological adverse reaction or “innate hypersensitivity”? *Int J Mol Sci* 2017;18:1223.