Anaphylaxis to Neuromuscular-blocking Drugs

All Neuromuscular-blocking Drugs Are Not the Same

Paul Michel Mertes, M.D., Ph.D., Gerald W. Volcheck, M.D.

IN the current issue of ANESTHESIOLOGY, Reddy *et al.*[1] report a two-hospital, retrospective, observational, cohort study confirming that anaphylaxis is more common with rocuronium and succinylcholine than with atracurium, a topic that is difficult to assess and was first highlighted in this journal in 2003.[2] Although any medication can potentially cause perioperative anaphylaxis, neuromuscular-blocking drugs (NMBDs), antibiotics, latex, and chlorhexidine are the most likely to do so. Regional differences regarding the relative risk of allergic reactions to NMBDs do exist. NMBDs represent the dominant causes of anaphylaxis in several countries and regions such as France,[2–4] Norway,[5] Spain,[6] and Australasia,[7] whereas other agents may be primarily involved in other countries.[8] Nevertheless, allergic reactions to NMBDs remain a serious concern for anesthesiologists because death may occur even when reactions are rapidly and adequately treated.[9] The reported incidence of perioperative anaphylaxis is quite varying, ranging between 1:3,500 and 1:20,000. Part of the variability is likely due to difficulty in determining the exact exposures to the numerous drugs, blood products, and agents used in the operative setting. The number of documented cases of intraoperative anaphylaxis is typically reported in aggregate for a large population, leaving the specifics of the total amount and type of medications the population was exposed to in question.

"There are many factors that will influence the choice of a specific NMBD, depending on the clinical situation, [including] the likely increased allergic risk associated with succinylcholine and rocuronium...."

In the study by Reddy *et al.*, the authors take the advantage of their ability to retrieve detailed information concerning new patient exposure to each NMBD from electronic anesthetic records available in the two participating centers over 7 yr. This allowed a more precise estimate of the number of patients exposed as the denominator when calculating the relative risk of allergic reactions associated with the use of each NMBD. This method helps eliminate the primary concern with data based on drug sales, which have the potential to overestimate the exposure resulting in a potential underestimation of anaphylaxis rate. Interestingly, the authors' findings are similar to the estimates of allergic reactions to NMBDs based on drug sales. This study confirms the increased relative risk of allergic reaction to succinylcholine and rocuronium in countries where a high rate of reaction to NMBDs is reported.

The surveillance of intraoperative adverse drug reactions still represents a clinical and statistical challenge[10] because these reactions are rare, random, and mostly independent from the repeated exposure of patients to anesthesia. In addition, possible biases and underreporting make comparison between drugs relatively difficult. Another weakness of any reporting system is that responsible physicians seem to have little understanding of which drug is actually causing the anaphylactic reaction when several drugs are simultaneously administered during anesthesia induction due to a lack of a single confirmatory test.[11] With thorough review in this study, it was noted that 9 of the 21 cases of identified NMBD anaphylaxis did not meet the standard skin test criteria for positivity but correctly warranted inclusion based on clinical picture and adjunct testing.

Because identification of the anaphylactic mechanism, of the responsible drug, and of the alternative safe agents is not always straightforward, a standard use of tryptase measurements in case of suspected allergic reactions and investigation of these reactions in compliance with established guidelines[12] by allergists trained in the field of drug allergy working in close collaboration with anesthesiologists should be promoted.[13,14] Reddy *et al.* confirm that

Image: ©Thinkstock.

Corresponding article on page 39.

Accepted for publication September 15, 2014. From the Strasbourg Medical School, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, Cedex, France (P.M.M.); and Mayo Medical School, Rochester, Minnesota (G.W.V.).

 Anesthesiology 2015; 122:5-7

allergic reactions are associated with greater tryptase and greater severity than nonallergic cases. Because no predictive test can help us to identify patients at risk before any reaction, reduction of the risk of perioperative anaphylaxis can only be based on secondary prevention.[12] This report provides a strong motivation for a thorough and systematic investigation of any hypersensitivity reactions occurring during the perioperative period[15] to avoid any undesirable subsequent exposure to an offending agent toward which one is already sensitized. This necessity is further supported by the small number of minor reactions diagnosed in this study, probably related to under-referral of mild reactions to all agents, a reality clearly demonstrated in the literature.[4,15] The authors were not able to determine the number of reactors who were receiving anesthesia for the first time, had a history of multiple anesthetic exposure or even history of previous reaction. This information would be helpful in future studies in determining sensitization patterns. Going forward, studies of intraoperative anaphylaxis should include a standard definition of anaphylaxis, uniform skin testing, specific immunoglobulin E drug testing, tryptase measurements, and review by an allergist in conjunction with an anesthesiologist.

The risk of allergic reactions is not the only drug characteristic that anesthesiologists must take into account when making their clinical choice. In view of the number of side effects associated with the use of succinylcholine, a controversy exists concerning replacing this old drug by rocuronium for rapid sequence induction.[16] Nevertheless, because of their rapid onset of effect, both drugs will remain essential in the anesthesiologists' armamentarium. Another interesting point that must be considered is that rocuronium can be rapidly reversed by sugammadex, a possibility that can make rocuronium a drug of choice in countries where sugammadex is available.[17] Sugammadex has also recently been proposed to improve recovery in case of anaphylaxis to rocuronium[18]; however, its ability to play a role in reaction reversal remains controversial.[19,20] Moreover, hypersensitivity reactions, either allergic or not, have been reported with sugammadex,[21] and this drug has not been approved in the United States at present.

Due to the amount of vecuronium exposures, Reddy *et al.* were not able to provide specific information concerning the risk associated with its use. This drug has been shown to have a lower risk of anaphylaxis than rocuronium in large epidemiologic studies[22] and its effect can also be effectively reversed by sugammadex.[23] They considered atracurium to be a safe alternative but were not able to comment on the relative risk associated with cisatracurium because this drug is not in use in Australasia. Cisatracurium has been shown to have the lowest risk of hypersensitivity reactions, either allergic or not, in large cohort studies,[3,22] and has also been shown to have the lowest rate of cross-sensitization with other NMBDs in allergic patients.[7,22] There are many factors that will influence the choice of a specific NMBD, depending on the clinical situation, but the likely increased allergic risk associated with succinylcholine and rocuronium, and the relatively low risk associated with atracurium and even more so with cisatracurium must be part of the clinical reasoning when considering the use of a NMBD.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Mertes: paul-michel.mertes@chru-strasbourg.fr

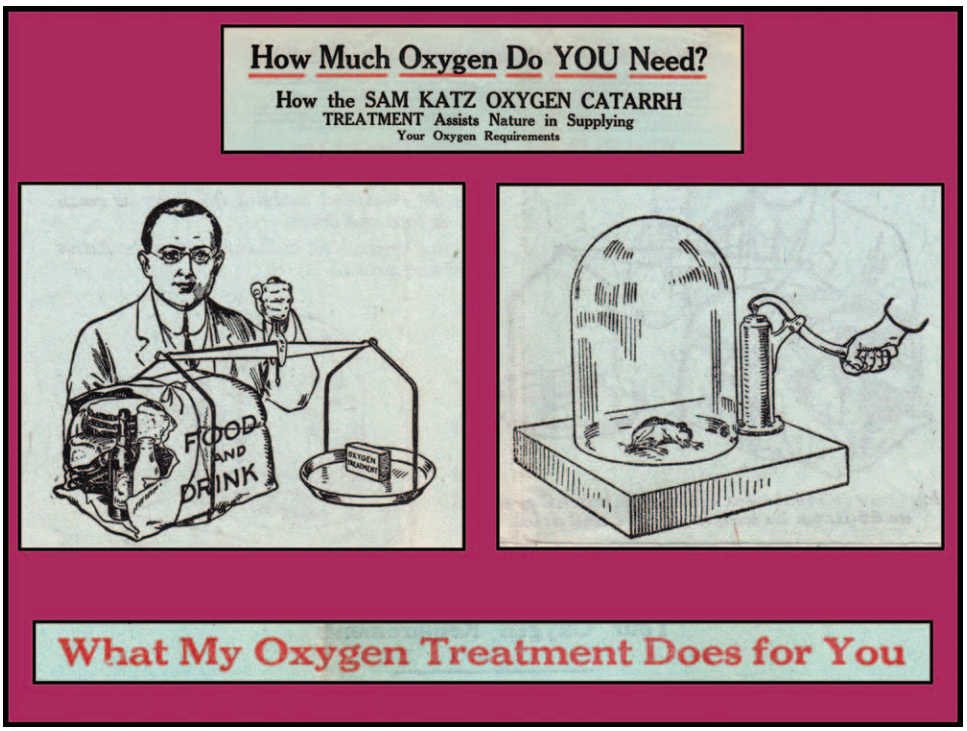
References

1. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ: Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. Anesthesiology 2015; 122:39–45
2. Mertes PM, Laxenaire MC, Alla F: Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. Anesthesiology 2003; 99:536–45
3. Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM; GERAP: Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005–2007). Minerva Anestesiol 2012; 78:868–78
4. Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques: Anaphylaxis during anesthesia in France: An 8-year national survey. J Allergy Clin Immunol 2011; 128:366–73
5. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E: Anaphylaxis during anesthesia in Norway: A 6-year single-center follow-up study. Anesthesiology 2005; 102:897–903
6. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, Gastaminza G, Martinez-Albelda I, González-Mahave I, Muñoz D: Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. J Investig Allergol Clin Immunol 2008; 18:350–6
7. Sadleir PH, Clarke RC, Bunning DL, Platt PR: Anaphylaxis to neuromuscular blocking drugs: Incidence and cross-reactivity in Western Australia from 2002 to 2011. Br J Anaesth 2013; 110:981–7
8. Gurrieri C, Weingarten TN, Martin DP, Babovic N, Narr BJ, Sprung J, Volcheck GW: Allergic reactions during anesthesia at a large United States referral center. Anesth Analg 2011; 113:1202–12
9. Reitter M, Petitpain N, Latarche C, Cottin J, Massy N, Demoly P, Gillet P, Mertes PM; French Network of Regional Pharmacovigilance Centres: Fatal anaphylaxis with neuromuscular blocking agents: A risk factor and management analysis. Allergy 2014; 69:954–9
10. Laake JH, Røttingen JA: Rocuronium and anaphylaxis—A statistical challenge. Acta Anaesthesiol Scand 2001; 45:1196–203
11. Krøigaard M, Garvey LH, Menné T, Husum B: Allergic reactions in anaesthesia: Are suspected causes confirmed on subsequent testing? Br J Anaesth 2005; 95:468–71
12. Mertes PM, Malinovsky JM, Jouffroy L, Aberer W, Terreehorst I, Brockow K, Demoly P; Working Group of the SFAR and SFA; ENDA; EAACI Interest Group on Drug Allergy: Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol 2011; 21:442–53

13. Mertes PM, Demoly P, Malinovsky JM: Hypersensitivity reactions in the anesthesia setting/allergic reactions to anesthetics. Curr Opin Allergy Clin Immunol 2012; 12:361–8
14. Volcheck GW, Mertes PM: Local and general anesthetics immediate hypersensitivity reactions. Immunol Allergy Clin North Am 2014; 34:525–46, viii
15. Malinovsky JM, Decagny S, Wessel F, Guilloux L, Mertes PM: Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. Acta Anaesthesiol Scand 2008; 52:175–81
16. Perry JJ, Lee JS, Sillberg VA, Wells GA: Rocuronium *versus* succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev 2008: CD002788
17. Aceto P, Perilli V, Modesti C, Ciocchetti P, Vitale F, Sollazzi L: Airway management in obese patients. Surg Obes Relat Dis 2013; 9:809–15
18. McDonnell NJ, Pavy TJ, Green LK, Platt PR: Sugammadex in the management of rocuronium-induced anaphylaxis. Br J Anaesth 2011; 106:199–201
19. Clarke RC, Sadleir PH, Platt PR: The role of sugammadex in the development and modification of an allergic response to rocuronium: Evidence from a cutaneous model. Anaesthesia 2012; 67:266–73
20. Leysen J, Bridts CH, De Clerck LS, Ebo DG: Rocuronium-induced anaphylaxis is probably not mitigated by sugammadex: Evidence from an *in vitro* experiment. Anaesthesia 2011; 66:526–7
21. Tsur A, Kalansky A: Hypersensitivity associated with sugammadex administration: A systematic review. Anaesthesia 2014; 69:1251–7
22. Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, Mouton-Faivre C, Audibert G, O'Brien J, Frendt D, Brezeanu M, Bouaziz H, Guéant JL: Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des 2008; 14:2809–25
23. Malinovsky JM, Plaud B, Debaene B, Mertes PM: [Do we know all indications and side effects of sugammadex?]. Ann Fr Anesth Reanim 2011; 30:709–10

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Katz Oxygen Treatment for Catarrh



Just before World War I, the company of Chicago's Samuel Katz peddled his "Oxygen Treatment for Catarrh" as an oxygenating panacea. He advertised that his cure-all contained "as much Oxygen as 86 times its weight in food and drink" (*left*). Katz reminded his readers that if they placed "any living thing in a vacuum, without oxygen … it will die" (*right*). In 1917 another Chicago-based organization, the American Medical Association (AMA) published analyses of Katz Oxygen Treatment revealing it to consist of four discrete boxes, consisting chiefly of (1) "aloes," (2) "magnesium dioxide, magnesium carbonate and … calcium salts, with acacia," (3) "sodium perborate and tartaric acid," and (4) "cotton soaked in menthol." So ironically, Chicago provided a home to promoters (Katz and Company) and discreditors (the AMA) of the Katz Oxygen Treatment.

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com

Anaphylaxis Is More Common with Rocuronium and Succinylcholine than with Atracurium

Jeffrey I. Reddy, F.A.N.Z.C.A., Peter J. Cooke, F.A.N.Z.C.A., Johan M. van Schalkwyk, F.R.A.C.P., Jacqueline A. Hannam, Ph.D., Penny Fitzharris, M.D., Simon J. Mitchell, Ph.D., F.A.N.Z.C.A.

ABSTRACT

Background: Intraoperative anaphylaxis is a rare but serious occurrence, often triggered by neuromuscular-blocking drugs (NMBDs). Previous reports suggest that the rates of anaphylaxis may be greater for rocuronium than for other NMBDs, but imprecise surrogate metrics for new patient exposures to NMBDs complicate interpretation.

Methods: This was a retrospective, observational cohort study of intraoperative anaphylaxis to NMBDs at two hospitals between 2006 and 2012. Expert anesthetic and immunologist collaborators investigated all referred cases of intraoperative anaphylaxis where NMBDs were administered and identified those where a NMBD was considered responsible. New patient exposures for each NMBD were extracted from electronic anesthetic records compiled during the same period. Anaphylaxis rates were calculated for each NMBD using diagnosed anaphylaxis cases as the numerator and the number of new patient exposures as the denominator.

Results: Twenty-one patients were diagnosed with anaphylaxis to an NMBD. The incidence of anaphylaxis was 1 in 22,451 new patient exposures for atracurium, 1 in 2,080 for succinylcholine, and 1 in 2,499 for rocuronium ($P < 0.001$).

Conclusions: In Auckland, the rate of anaphylaxis to succinylcholine and rocuronium is approximately 10-fold higher than to atracurium. Previous estimates of NMBD anaphylaxis rates are potentially confounded by inaccurate proxies of new patient exposures. This is the first study to report anaphylaxis rates using a hard denominator of new patient exposures obtained directly from anesthetic records. **(Anesthesiology 2015; 122:39-45)**

INTRAOPERATIVE anaphylaxis is a rare but serious event that may cause significant morbidity and mortality.[1–3] Neuromuscular-blocking drugs (NMBDs) are common causative agents during anesthesia.[2,4–8] There is controversy whether the incidence of anaphylaxis is higher with rocuronium than with other NMBDs. Evidence that this might be so has been reported from France,[1,6] Norway,[5,9] and some parts of Australia,[4,7] whereas no difference has been found from the limited data available for the United States.[10]

Such comparisons are complicated by difficulties in obtaining accurate numerator and denominator data with which to calculate an incidence for the various drugs. Deriving accurate numerators relies on capture of all relevant anaphylaxis cases and thorough and consistent case investigation. Denominators based on cases actually exposed to each agent are even harder to obtain because of the difficulties associated with retrieval of administration records from many thousands of anesthetics. For the latter reason, relevant denominators have usually been estimated from sales data or similar metrics that fail to account for confounders such as vials opened but not used, discarded date-expired vials, and repeat administrations or infusions. These problems, combined with the previously mentioned potential for geographical variation, result in divergent estimates of anaphylaxis incidence for the same drug. For example, the reported incidence of anaphylaxis to rocuronium varies from approximately 1:3,500 to 1:445,000.[5,11]

What We Already Know about This Topic

- Neuromuscular-blocking drugs are common causative agents of intraoperative anaphylaxis
- Comparisons of neuromuscular-blocking drug anaphylaxis rates are complicated by difficulties in obtaining accurate numerator and denominator data

What This Article Tells Us That Is New

- Search of a database containing more than 400,000 anesthetic records identified 92,858 new patient exposures to neuromuscular-blocking drugs between 2006 and 2012
- Twenty-one of 89 patients referred to the Anaesthetic Allergy Clinic had anaphylaxis attributed to muscle relaxants
- Use of credible numerator and denominator data found similar rates of anaphylaxis after succinylcholine and rocuronium administration, rates that were nearly an order of magnitude higher than those for atracurium and other neuromuscular-blocking drugs

We undertook a 7-yr retrospective review of the incidence of intraoperative anaphylaxis to NMBDs in Auckland, New

Corresponding article on page 5. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication March 18, 2014. Accepted for publication August 11, 2014. From the Department of Anaesthesia and Perioperative Medicine, North Shore Hospital, Auckland, New Zealand (J.I.R.); Department of Anaesthesia and Perioperative Medicine (P.J.C., J.M.v.S.) and Department of Immunology (P.F.), Auckland City Hospital, Auckland, New Zealand; and Department of Anaesthesiology (J.A.H., S.J.M.), University of Auckland, Auckland, New Zealand.

 Anesthesiology 2015; 122:39-45

Zealand. All cases of intraoperative anaphylaxis in the city were referred to a single clinic for investigation, facilitating capture of cases. Moreover, hospital catchment areas are strictly defined and maintained, and two of the three large hospitals in the city used an electronic system to record all anesthetics during this 7-yr period. The associated database contains more than 400,000 anesthetic records which can be searched for administration of particular drugs. These local practices provide accurate numerators and denominators for the calculation of anaphylaxis rates for anesthetic drugs. We compared anaphylaxis rates for various NMBDs, with the null hypothesis being that there is no difference in anaphylaxis rates between agents.

Materials and Methods

This retrospective, observational cohort study was approved by the Health and Disability Ethics Committee (Reference: 12/NTA/65) and institutional approval was granted by Auckland District Health Board (Auckland, New Zealand) and Waitemata District Health Board (Auckland, New Zealand). Approval was also granted to release the full, anonymized dataset.

Denominator Data

Auckland City Hospital and North Shore Hospital are the two principal public hospitals within Auckland District Health Board and Waitemata District Health Board, respectively. Both hospitals use the SAFERsleep™ electronic anesthetic record keeping and safety system (SAFERSleep: Safer Sleep LLC, Nashville, TN).[12] This system was fully implemented in all theaters before the study period from January 1, 2006 to December 31, 2012. All drug administrations during an anesthetic are entered by the anesthesiologist using either bar code scanning of specific drug labels on syringes or manual entry (*via* a keyboard) and are permanently recorded by the system.

SAFERsleep maintains anesthetic records in a secure database. Using relevant search criteria in Structured Query Language, we identified all anesthetics in which NMBDs were used. For each record, we extracted the patient's unique National Health Index number, sex, age, name of NMBD used, total number of administrations of NMBD, and use of infusions. After excluding duplication of patients undergoing multiple procedures, we calculated the number of new patient exposures to each NMBD. A new patient exposure was defined as the administration of an NMBD to a patient, for the first time (during the study period). That is, if the same patient received the same NMBD during one or more anesthetics, a single new exposure was considered to have occurred during the period of analysis.

Numerator Data

The Auckland Anesthetic Allergy Clinic is a multidisciplinary clinic staffed by anesthesiologists, immunologists, and immunology technologists. Case referrals listed all medications and substances administered before the episode of anaphylaxis, the clinical features, and details of treatment. The anesthetic record was also attached. Patients were seen at the clinic approximately 6 weeks after receipt of referral for consultation and skin testing. The consultation elucidated any other relevant history and established the patient's fitness and consent for skin testing. Skin testing was carried out according to the clinic's protocol which is based on the methodology first described by Fisher and Bowey.[13] The clinical features, serial tryptase results, specific immunoglobulin E testing, and skin testing were then used to confirm the diagnosis and identify the likely causative agent. All medications administered before the anaphylaxis were tested. All patients had skin testing for chlorhexidine (skin prick test 2% aqueous) and latex.

Intradermal skin testing was generally performed on the patient's back. A volume of 0.02 ml of each drug was injected intradermally, and the size of the wheal was measured with calipers after 15 min for comparison with the size of the wheal produced by the injection of 0.02 ml of 0.9% saline (negative control). The test was regarded as positive if the wheal diameter obtained with the drug was larger than the negative control wheal by 3 mm or more. The test was regarded as equivocal if the wheal diameter increased by 1 to 2 mm, with a surrounding flare. A skin prick test with histamine 10 mg/ml was used as a positive control. The drug dilutions used for intradermal testing of muscle relaxants are provided in table 1. If any muscle relaxant had been administered, skin tests were carried out with the full range of muscle relaxants available to detect cross-sensitization.

We included all patients from the two hospitals who were referred after intraoperative anaphylaxis and who had received NMBDs during the study period. Relevant correspondence, referral forms, anesthetic records, and the skin testing results were examined. All the cases were reviewed independently by an anesthetist and an immunologist and then discussed. In the cases confirmed as NMBD-induced allergic anaphylaxis, severity grading was made according to the guidelines published by Mertes *et al.* (table 2).[14] Peak serum tryptases were also recorded.

Diagnostic classification of the patients was based on clinical consensus on all of the following points:

1. Whether or not the patient had one or more manifestations of anaphylaxis as described by Mertes *et al.*[14];
2. The temporal relation between the administration of an NMBD and the onset of anaphylaxis;
3. The supporting laboratory evidence of allergic anaphylaxis to the relevant NMBD based on intradermal testing with NMBDs, the serum tryptase result, and specific immunoglobulin E testing when available;
4. Ensuring that skin testing had been carried out for other substances or medications that may have caused the anaphylaxis.

Where skin testing (described earlier in this section) was equivocal, all the above features were used to determine

Table 1. Drug Dilutions Used for Intradermal Testing

Drug	Concentration	
Succinylcholine	0.05 mg/ml	1:1,000 dilution of 100 mg in 2 ml
Mivacurium	0.0002 mg/ml	1:10,000 dilution of 10 mg in 5 ml
Atracurium	0.001 mg/ml	1:10,000 dilution of 50 mg in 5 ml
Pancuronium	0.002 mg/ml	1:1,000 dilution of 4 mg in 2 ml
Vecuronium	0.004 mg/ml	1:1,000 dilution of 4 mg in 1 ml
Rocuronium	0.01 mg/ml	1:1,000 dilution of 50 mg in 5 ml
Saline (negative control)	0.9%	

Table 2. Clinical Grading of Anaphylaxis

Grade	Symptoms
1	Cutaneous signs: generalized erythema, urticaria, angioedema
2	Measurable but not life-threatening symptoms: cutaneous signs, hypotension, tachycardia Respiratory disturbances: cough, difficulty inflating
3	Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm
4	Cardiac and/or respiratory arrest

Adapted from Mertes *et al*. J Investig Allergol Clin Immunol 2011; 21:442–53.[14] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

the cause, as is appropriate in clinical decision making. It is important to emphasize that no one test unequivocally allows diagnosis of anaphylaxis to NMBDs. It is difficult to use a rigid case definition with the sensitivity and specificity of all the available tests being incompletely understood.

Statistical Analysis

The rate of anaphylaxis to NMBDs was calculated using confirmed cases of anaphylaxis to each drug as the numerator and the number of new patient exposures to the drug as the denominator. Fisher exact test was used to compare the incidence of anaphylaxis to the various NMBDs during the entire interval. CI (95%) were calculated based on the Poisson distribution. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were conducted in R, version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). Because of the large numbers in the denominator, P values for Fisher exact test were computed using Monte Carlo simulation with 10^7 replicates. Additional details of our statistical analysis are given in Supplemental Digital Content 1, http://links.lww.com/ALN/B110.

Results

During the 7-yr period from January 1, 2006 to December 31, 2012, there were 92,858 new patient exposures to NMBDs. Database queries and analyses are available in Supplemental Digital Content 2, http://links.lww.com/ALN/B111. The full (deidentified) dataset is available online.* Eighty-nine of these patients were referred to the Anesthetic Allergy Clinic for follow-up investigation of an intraoperative event that was thought to be anaphylaxis (table 3).

Two referred cases did not attend the clinic and were lost to follow-up. In five cases, we excluded anaphylaxis with a high level of certainty on historical grounds, and in 36 cases with negative skin testing, a diagnosis of nonallergic (nonimmunoglobulin E mediated) anaphylaxis was made. In 25 cases, the causative agent was identified as a substance other than a muscle relaxant (chlorhexidine 8, cefazolin 7, *Gelofusine*® 5, latex 1, tramadol 1, diclofenac 1, paracetamol 1, and protamine 1). Twenty-one cases of allergic anaphylaxis were attributed to muscle relaxants. Table 3 summarizes these cases and lists all use of muscle relaxants in all cases, including those cases lost to follow-up and those considered either due to nonallergic anaphylaxis or not to represent anaphylaxis at all.

Demographics and clinical features of these 21 cases are shown in table 4. The average age of patients was 59 yr and females accounted for 17 of 21 (81%) cases. Four cases were categorized as clinical grade 2, 12 as grade 3, and 5 as grade 4. The median peak tryptase level was 59 μg/l (range, 7.8 to >200 μg/l), with only one patient (20) having a tryptase of

Table 3. Classification of Patients Referred to the Anesthetic Allergy Clinic and Muscle Relaxants Received

	Count
Nonallergic anaphylaxis	
Atracurium	11
Succinylcholine	12
Succinylcholine and atracurium	2
Pancuronium	1
Vecuronium	2
Rocuronium	8
Total	36
Did not attend clinic	
Atracurium	1
Succinylcholine	1
Total	2
Allergic anaphylaxis to a muscle relaxant	
Atracurium	3
Rocuronium	6
Succinylcholine	12
Total	21
Allergic anaphylaxis to drugs that are not muscle relaxants:	25
Not allergy	
Atracurium	1
Succinylcholine	2
Succinylcholine and atracurium	1
Rocuronium	1
Total	5
Grand total	89

* Available at: http://www.anaesthetist.com/R/allergy2014/nmba_anaphylaxis_supplement_3.zip. Accessed June 19, 2014.

Table 4. Clinical Features of Cases with Anaphylaxis to Neuromuscular-blocking Drugs

Case	Index Drug	Age (yr)	Sex	Grade	Tryptase (peak: μg/l)	Wheal/Flare Size (mm)		Positive by Skin Test Criteria	Cross-sensitivity	Prominent Clinical Features	Notes
						Saline	Relaxant				
1	sux	64	F	2	49	7	7/0	No		HYT, BSM, HYPOX, R	+IgE succinylcholine, negative ID test
2	roc	69	F	3	37.2	7	10/25	Yes	vec	HYT, BSM, R, arrhythmia	
3	sux	70	F	4	>200	7	12/29	Yes		HYT, BSM, R, BRADY	
4	roc	78	F	4	147	9	10/32	No		HYT, BSM, HYPOX, R	ID equivocal, strongly positive clinical features
5	roc	70	M	2	16.3	7	7/10	No	sux	HYT, R	On retest rocuronium 8/30 saline 6 mm, equivocal
6	sux	41	F	3	127	6	10/35	Yes	roc	HYT, BSM, TACHY	+IgE succinylcholine
7	roc	46	M	3	154	7	9/31	No	vec, sux	HYT, BSM, TACHY, HYPOX, R	ID equivocal, multiple other positives
8	sux	56	F	3	63	6	9/59	Yes		HYT, HYPOX, TACHY	
9	atrac	67	M	2	76	6	8/12	No		HYT, R	Systemic mastocytosis
10	sux	65	F	3	174	7	11/196	Yes	miv, atrac	HYT, BSM, R	
11	sux	49	M	2	22.8	7	12/81	Yes		HYT, BSM, R	
12	roc	96	F	4	30.4	6	8/23	No	vec, panc	HYT, TACHY, R	ID equivocal, multiple other positives
13	sux	36	F	3	38	5	13/53	Yes		HYT, BSM, HYPOX, R	+IgE succinylcholine
14	sux	69	F	3	16.5	7	7/56	No	roc	HYT, BSM, HYPOX, R, urticaria	+IgE succinylcholine, ID for rocuronium positive
15	sux	31	F	3	58.5	8	12/35	Yes		HYT, BSM, FS	
16	sux	65	F	3	79.3	8	14/40	Yes	vec	HYT, TACHY, R	
17	atrac	32	F	3	39.6	7	9/35	No		HYT, TACHY, R	ID equivocal, strongly positive clinical features
18	sux	66	F	4	>200	7	16/32	Yes		HYT, R	
19	sux	50	F	3	67.8	8	13/32	Yes		HYT, R	
20	roc	50	F	3	7.8	6	12/125	Yes	sux, vec	HYT, BSM, TACHY, R	
21	atrac	65	F	4	59	7	6/0	No		HYT, TACHY, flushing, ventricular fibrillation	Severe anaphylaxis × 2 related to atracurium, retested 6/0

atrac = atracurium; BRADY = bradycardia; BSM = bronchospasm; FS = facial swelling; HYPOX = hypoxemia; HYT = hypotension; ID = intradermal; IgE = immunoglobulin E; miv = mivacurium; panc = pancuronium; R = rash; roc = rocuronium; sux = suxamethonium; TACHY = tachycardia; vec = vecuronium.

less than 12 μg/l. This compared with a median peak tryptase of 7.5 μg/l (range, 1 to 33.2 μg/l) in the group with nonallergic anaphylaxis, which also exhibited lower severity scores (4 were grade 1, 20 were grade 2, and 12 were grade 3).

Nine of the 21 cases of allergic anaphylaxis did not meet the standard skin test criteria but were nevertheless considered to warrant inclusion on careful consideration of the clinical picture and relevant tests. The notes on the right hand side of table 4 give an indication as to why this diagnosis was made, despite the absence of a wheal increase of 3 mm or more in these nine cases. Two succinylcholine cases (1, 14) showed the presence of immunoglobulin E antibodies specific for succinylcholine with one (14) also showing cross-sensitization to rocuronium (which had not been administered). Three rocuronium patients (5, 7, and 12) with equivocal skin tests were cross-sensitized to various other NMBDs (not administered). One patient (21) with negative skin tests to atracurium experienced further anaphylaxis on reexposure

Table 5. Intraoperative Incidence of Neuromuscular-blocking Drug-related Anaphylaxis

	Succinylcholine	Rocuronium	Atracurium	Other
Anaphylaxis	12	6	3	0
95% CI (Poisson)	6–21	2–13	0–9	0–4
Exposure	24,960	14,995	67,354	15,042
Rate	1:2,079	1:2,498	1:22,450	—
Range (from CI)	1:1,190–4,030	1:1,150–6,810	1:7,680–109,000	1:4,080–∞

to atracurium. One rocuronium (4) and two atracurium (9, 17) patients showed a 1 to 2-mm wheal increase, with flare, no other cause, positive tryptase and timing consistent with the NMBD being causative. Cross-sensitization was demonstrated overall in 9 of the 21 cases (43%).

The number of new patient exposures, number of confirmed cases of anaphylaxis, and rates of confirmed anaphylaxis to succinylcholine, rocuronium, atracurium, and a composite of other NMBDs (vecuronium, pancuronium, and mivacurium) are shown in table 5. These data suggest that there is a large (10-fold) difference between the rate for atracurium and the rates for succinylcholine and rocuronium ($P < 0.001$). Unsurprisingly, individual 2×2 comparisons reveal that the differences reside in the rates of anaphylaxis to succinylcholine and rocuronium compared with the other agents. For example, the *P* value for rocuronium *versus* atracurium is approximately 0.002.

To test the robustness of our results, we performed two main sensitivity analyses. In the first analysis, we assumed a worst-case scenario: anaphylaxis to NMBDs in all patients who either did not attend or are labeled as "nonallergic anaphylaxis" in table 3. Rates of anaphylaxis to succinylcholine, rocuronium, atracurium, and other agents are then 1:920, 1:1,070, 1:5,000, and 1:4,000, respectively. We did not observe any cases of anaphylaxis to vecuronium in our dataset (0 of 9,585 new exposures). Application of Fisher test as before still results in rejection of the null hypothesis at a *P* value of 6×10^{-7}.

The second "restrictive" sensitivity analysis took the opposite approach, rejecting all cases in table 4 that do not strictly conform to "standard criteria" and abandoning the clinical judgment of the anesthesiologist and immunologist who assessed the cases. Even here, a *P* value of 2×10^{-6} mandates rejection of the null hypothesis although the difference is then mainly due to succinylcholine.

Discussion

The principal finding of this study was that in the Auckland region, the use of succinylcholine and rocuronium was associated with a substantially higher rate of intraoperative anaphylaxis compared with atracurium and other NMBDs. There was similarity between the incidence of anaphylaxis to rocuronium and succinylcholine (approximately 1:2,500 and 1:2,000, respectively); in contrast, the rate of anaphylaxis to atracurium was substantially lower (1:22,000). This difference is unlikely to be an artifact due to the large numbers in the denominators, and this observation is supported by several large European studies.[1,6,8] No cases of anaphylaxis were observed for vecuronium (0 of 9,585 new exposures). The proportion of anaphylaxis events during anesthesia resulting from sensitization to NMBDs (46%) is similar to that reported in France, Norway, Spain, and Australia.[2,4–8,15] The characterization of our patient series, with 56% of anaphylaxis cases being found to be allergic and associated with higher tryptase and greater severity than nonallergic cases, is similar to that in other published studies.[1,2,4,8]

The study provides direct calculation of comparative rates of anaphylaxis based on actual measurement of denominator data. Previous studies have used surrogate denominators based on metrics such as drug sales data, which are prone to inaccuracies. The use of drug sales as an index of patient exposures is confounded by the discarding of expired drugs, multiple administrations, and infusions in long cases. Wastage of NMBDs can be substantial, suggesting that denominators based on drug sales or supply may substantially overestimate exposure, resulting in a potential underestimation of anaphylaxis rates. Notwithstanding such concerns, other studies have reported a higher rate for anaphylaxis to rocuronium than to other nondepolarizing NMBDs,[1,4–7] in agreement with the results from our region.

This finding will likely give anesthetists pause to consider the place of rocuronium in their clinical armamentarium. It is a popular drug for a variety of reasons, not least of which is that it exhibits the fastest onset of all the nondepolarizing NMBDs and it can be used as an acceptable substitute for succinylcholine in a rapid sequence induction. A further reason to use rocuronium in the latter application, despite slower onset when compared with succinylcholine,[16] may be that its effect can be rapidly reversed by sugammadex. Other than to discourage the selection of rocuronium over succinylcholine on the basis of a lower risk of anaphylaxis, our finding is unlikely to change the use of rocuronium in rapid sequence inductions because there are still many reasons why succinylcholine may be contraindicated or why anesthetists may prefer to avoid it. The present authors would have no hesitation in using rocuronium under such circumstances. In contrast, our findings suggest that when all other factors are equal, it may be prudent to reconsider the use of rocuronium in routine cases where it is not being used for any of its particular properties, at least in those regions where there is some evidence that sensitivity is prevalent. Atracurium seems a safer alternative, and although we cannot comment on the basis

of our data which contained too few vecuronium exposures, others have also shown vecuronium to be safer.[1,6,7]

There are several potential limitations to our study. First, the data are limited to the Auckland region of New Zealand and the results can only be extrapolated to other regions and nations with caution. Geographical differences in sensitivity to NMBDs are likely to be real and may be based on regional differences in exposure to other sensitizers such as pholcodine.[17,18]

Second, studies of this nature are vulnerable to any systematic error that leads to an unequal likelihood of identifying cases due to one drug relative to others. In our study, such errors would be possible either in the selection of cases for referral to the regional anesthetic allergy clinic or in the clinical evaluation of the cause of anaphylaxis.

Regarding potential referral errors, despite the single anesthetic allergy clinic in the Auckland region, it is possible that some patients with anaphylactic reactions were not referred from study hospitals for evaluation at the clinic. However, this would represent a serious departure from mandated practice at these institutions (or indeed from accepted anesthetic practice anywhere). Moreover, there is no convincing reason to suspect that any such departures would favor one drug. One possible concern is that the well-understood propensity for atracurium to cause histamine release may have inclined anesthesiologists to overlook anaphylaxis of a minor degree related to this agent, but the severity grading of the identified reactions (table 3) appears balanced across agents and therefore does not support this hypothesis. We do acknowledge that there may have been underreferral of minor reactions to all agents, as there were few grade 1 reactions diagnosed in the study.

In respect of potential evaluation errors, the evaluation of referred cases at the clinic followed a standard protocol (outlined earlier) including application of a consistent case definition, and the determination of causation for each case reported in this study was independently reviewed by an anesthetic allergy specialist and an immunologist. Although it is acknowledged that there is variation in the way in which the clinical histories, skin testing results, and other tests are evaluated, there is widespread acceptance that all features should be considered in diagnosis.[19] All the relevant clinical features and available test results have been transparently provided. It was not always possible to identify the agent on skin testing even though there was a convincing history of anaphylaxis. In 46 cases, the drug or substance was identified on skin testing, but in 36 cases (44%), it was not. This reaction rate is consistent with other large surveys.[1,3]

Third, there is a small potential for inaccuracies in the denominator data and the other associated data gathered from the electronic database of anesthetic records. For example, the records rely on anesthesiologists entering details such as the drug type and dose. These details are checked intra- and postoperatively and a printout requiring a signature by the anesthesiologist certifies this as a legal record of the procedure. Previous research in our institution, which took place during the period of the current study, demonstrated a rate of omission of drug administration from the electronic record of 2.31 per 100 drug administrations.[20] Finally, we did not formally account for the increased risk of family-wise error rate by correcting our *P* values for multiple testing; this topic is further explored in Supplemental Digital Content 1, http://links.lww.com/ALN/B110.

In conclusion, we have used credible numerator and denominator data to demonstrate similar rates of anaphylaxis after administration of succinylcholine and rocuronium—these rates were approximately an order of magnitude higher than those for atracurium and other nondepolarizing NMBDs. Rocuronium remains a useful alternative to succinylcholine in rapid sequence inductions where succinylcholine is contraindicated, but its routine use as a muscle relaxant in preference to other NMBDs deserves careful consideration, particularly, in regions where presensitization is thought to be common.

Acknowledgments

The authors thank Ann Wills, F.A.N.Z.C.A., Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand, for her work in initiating data collection at the Anaesthetic Allergy Clinic; and Roy The, B.Sc., Immunopathology Department, Auckland City Hospital, for preparing the dilutions and administering the skin tests.

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Reddy: Department of Anaesthesia, North Shore Hospital, 124 Shakespeare Road, Takapuna, Auckland 0620, New Zealand. jeffrey.reddy@waitematadhb.govt.nz. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Mertes PM, Laxenaire MC, Alla F: Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. Anesthesiology 2003; 99:536–45
2. Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, Mouton-Faivre C, Audibert G, O'Brien J, Frendt D, Brezeanu M, Bouaziz H, Guéant JL: Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des 2008; 14:2809–25
3. Gibbs NM, Sadleir PH, Clarke RC, Platt PR: Survival from perioperative anaphylaxis in Western Australia 2000–2009. Br J Anaesth 2013; 111:589–93
4. Brereton A, Russell WJ: Anaphylaxis to muscle relaxants: An audit of ten years of allergy testing at the Royal Adelaide Hospital. Anaesth Intensive Care 2012; 40:861–6
5. Laake JH, Røttingen JA: Rocuronium and anaphylaxis—A statistical challenge. Acta Anaesthesiol Scand 2001; 45:1196–203

6. Laxenaire MC, Mertes PM; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques: Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth 2001; 87:549–58
7. Sadleir PH, Clarke RC, Bunning DL, Platt PR: Anaphylaxis to neuromuscular blocking drugs: Incidence and cross-reactivity in Western Australia from 2002 to 2011. Br J Anaesth 2013; 110:981–7
8. Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques: Anaphylaxis during anesthesia in France: An 8-year national survey. J Allergy Clin Immunol 2011; 128:366–73
9. Florvaag E, Johansson SG, Oman H, Venemalm L, Degerbeck F, Dybendal T, Lundberg M: Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. Acta Anaesthesiol Scand 2005; 49:437–44
10. Bhananker SM, O'Donnell JT, Salemi JR, Bishop MJ: The risk of anaphylactic reactions to rocuronium in the United States is comparable to that of vecuronium: An analysis of food and drug administration reporting of adverse events. Anesth Analg 2005; 101:819–22
11. Guttormsen AB: Allergic reactions during anaesthesia—Increased attention to the problem in Denmark and Norway. Acta Anaesthesiol Scand 2001; 45:1189–90
12. Merry AF, Webster CS, Mathew DJ: A new, safety-oriented, integrated drug administration and automated anesthesia record system. Anesth Analg 2001; 93:385–90
13. Fisher MM, Bowey CJ: Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. Br J Anaesth 1997; 79:59–63
14. Mertes PM, Malinovsky JM, Jouffroy L, Aberer W, Terreehorst I, Brockow K, Demoly P; Working Group of the SFAR and SFA; ENDA; EAACI Interest Group on Drug Allergy: Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol 2011; 21:442–53
15. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, Gastaminza G, Martinez-Albelda I, González-Mahave I, Muñoz D: Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. J Investig Allergol Clin Immunol 2008; 18:350–6
16. Perry JJ, Lee JS, Sillberg VA, Wells GA: Rocuronium *versus* succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev 2008: CD002788
17. Johansson SG, Florvaag E, Oman H, Poulsen LK, Mertes PM, Harper NJ, Garvey LH, Gerth van Wijk R, Metso T, Irgens A, Dybendal T, Halsey J, Seneviratne SL, Guttormsen AB: National pholcodine consumption and prevalence of IgE-sensitization: A multicentre study. Allergy 2010; 65:498–502
18. Florvaag E, Johansson SG: The pholcodine story. Immunol Allergy Clin North Am 2009; 29:419–27
19. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ: Anaphylaxis during anaesthesia: Diagnostic approach. Allergy 2007; 62:471–87
20. Merry AF, Webster CS, Hannam J, Mitchell SJ, Henderson R, Reid P, Edwards KE, Jardim A, Pak N, Cooper J, Hopley L, Frampton C, Short TG: Multimodal system designed to reduce errors in recording and administration of drugs in anaesthesia: Prospective randomised clinical evaluation. BMJ 2011; 343:d5543

Anaphylaxis Incidence with Rocuronium, Succinylcholine, and Atracurium: How Risk Communication Can Influence Behavior

To the Editor:

Reddy *et al.*[1] studying neuromuscular-blocking drug (NMBD)-induced perioperative anaphylaxis concluded that *"the rate of anaphylaxis to succinylcholine and rocuronium is approximately 10-fold higher than to atracurium."* However, we believe that major methodological issues should be highlighted in this article as the authors' resulting statement might mislead clinical care.

First, a small series including 21 cases of NMBD-induced allergic anaphylaxis among 89 patients who were referred to the Anesthetic Allergy Clinic during a 7-yr study period was presented, but NMBD-induced anaphylaxis was not proven in 9 of these 21 reported cases (42.8%) as skin tests remained negative to the culprit NMBD. Except in one case (patient 9 with mastocytosis), the negative skin tests to the culprit NMBD in the eight remaining cases including succinylcholine (n = 2), rocuronium (n = 4), and atracurium (n = 2) may be explained by false-negative results as follows. Only intradermal tests (IDTs) to NMBDs were performed, whereas optimal investigation of drugs should be performed by prick-tests followed by IDTs without exceeding the maximal concentrations. Accordingly, IDTs are more sensitive but less specific than prick-tests.[2–7] In addition, lower concentrations of NMBDs, that is, up to 100-fold lower, were used than those currently recommended in Europe[8] and in France,[7] explaining that one patient (patient 21) experienced further anaphylaxis on reexposure to atracurium despite negative skin tests to atracurium. Anaphylaxis to NMBD after negative skin testing has been previously reported by Fisher *et al.*[9] and Fraser and Smart[10] using the same drug dilutions and skin-testing protocol. We thus respectfully disagree with the authors who claim that "*no one test unequivocally allows diagnosis of anaphylaxis to NMBDs*" because skin testing is the definitive standard for the detection of anaphylaxis mediated by type E immunoglobulin (IgE) and the assessment of cross-reactive drugs and safe alternative regimens.[3–5,7,11]

Second, despite negative skin tests to the culprit NMBD, these patients were nonetheless considered to *"warrant inclusion on consideration of the clinical picture and relevant tests including serum tryptase and specific immunoglobulin E testing when available."* Although the measurement of tryptase concentration is a very valuable tool to support the diagnosis of IgE-mediated anaphylaxis,[3,5,7,11] identification of serum IgE to succinylcholine in two patients (patients 1 and 14) with negative skin tests to succinylcholine provides possible evidence of IgE sensitization but does not confirm that the drug induced the immediate reaction *per se*.[2,5]

Precisely, only the suxamethonium-specific assay is commercially available among the different NMBDs.[2]

Third, one of these patients (patient 9) with negative skin tests had systemic mastocytosis and received atracurium. In this case, moderate features including hypotension and rash associated with an increased tryptase level and negative skin tests to atracurium rather suggest nonallergic immediate hypersensitivity. Unfortunately, increase in tryptase level was not compared with the patient's baseline level that may be markedly increased in systemic mastocytosis,[12] whereas skin tests should also have been performed until the maximal recommended concentration.[7,8] Indeed, mastocytosis is not a risk factor for perioperative drug-induced IgE-mediated anaphylaxis, and mast cell degranulation usually occurs secondary to a variety of nonimmune triggers specific for each patient. The best way to avoid mast cell degranulation in mastocytosis is therefore to avoid potential triggers including histamine-releasing benzylisoquinolins, such as atracurium and mivacurium.[12]

Thus, in this series, only 12 cases of NMBDs-induced anaphylaxis can be considered to be definitively supported by positive skin tests including suxamethonium (n = 10) and rocuronium (n = 2). The claim that *"the rate of anaphylaxis to succinylcholine and rocuronium is approximately 10-fold higher than to atracurium"* should therefore be softened because this has not been proved while one should keep in mind that all NMBDs may elicit anaphylaxis.[4]

Besides, effective risk communication must take into account how various publics perceive risk influenced by societal and cultural factors rather than just focusing on science.[13] The last French survey of anesthesia-related mortality demonstrated that 3% of anesthesia-related deaths involved either NMBDs-induced or antibiotics-induced anaphylaxis, whereas 20% were due to pulmonary aspiration in 1999.[14] The analysis of aspiration-related deaths in surgical patients with known full stomach (26 cases) showed significant deviations from standard practices. Particularly, succinylcholine was not used by French anesthetists in two third of these patients. The expert panel suggested that the most common interpretation of this limited use of succinylcholine may be explained by the fear of the risk of succinylcholine-induced anaphylaxis largely publicized in France since the 1980s.[15] Thus, the risk communication on NMBD-induced anaphylaxis brought to the foreground a more severe adverse event such as pulmonary aspiration. This emphasizes the complicated process of disseminating risk messages.

In conclusion, the statement that *"anaphylaxis is more common with rocuronium and succinylcholine than with atracurium"* has not yet been proven and we believe that such a message is hazardous because it may have deleterious influences on anesthetists' behavior.

Competing Interests

Dr. Dewachter received symposium and lecture travel fees from MSD France, Courbevoie, France. Dr. Mouton-Faivre declares no competing interests.

This letter was sent to the author of the original article referenced above, who declined to respond.

Pascale Dewachter, M.D., Ph.D., Claudie Mouton-Faivre, M.D. Service d'Anesthésie-Réanimation Chirurgicale, Groupe Hospitalier de Paris-Seine Saint Denis, AP-HP, Paris, France (P.D.). pascale.dewachter@yahoo.fr

References

1. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ: Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. Anesthesiology 2015; 122:39–45
2. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ: Anaphylaxis during anaesthesia: Diagnostic approach. Allergy 2007; 62:471–87
3. Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, Harboe T, Eriksson LI, Dahlgren G, Seeman-Lodding H, Takala R, Wattwil M, Hirlekar G, Dahlén B, Guttormsen AB: Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. Acta Anaesthesiol Scand 2007; 51:655–70
4. Dewachter P, Mouton-Faivre C, Emala CW: Anaphylaxis and anesthesia: Controversies and new insights. Anesthesiology 2009; 111:1141–50
5. Harper NJ, Dixon T, Dugué P, Edgar DM, Fay A, Gooi HC, Herriot R, Hopkins P, Hunter JM, Mirakian R, Pumphrey RS, Seneviratne SL, Walls AF, Williams P, Wildsmith JA, Wood P, Nasser AS, Powell RK, Mirakhur R, Soar J; Working Party of the Association of Anaesthetists of Great Britain and Ireland: Suspected anaphylactic reactions associated with anaesthesia. Anaesthesia 2009; 64:199–211
6. Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugué P, Friedmann PS, English JS, Huber PA, Nasser SM; BSACI: BSACI guidelines for the management of drug allergy. Clin Exp Allergy 2009; 39:43–61
7. French Society of Anesthesiology and Intensive Care Medicine and French Society of Allergology: Reducing the risk of anaphylaxis during anaesthesia: Short text. Ann Fr Anesth Reanim 2011; 30:212–22
8. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, Bircher A, Blanca M, Bonadonna B, Campi P, Castro E, Cernadas JR, Chiriac AM, Demoly P, Grosber M, Gooi J, Lombardo C, Mertes PM, Mosbech H, Nasser S, Pagani M, Ring J, Romano A, Scherer K, Schnyder B, Testi S, Torres M, Trautmann A, Terreehorst I; ENDA/EAACI Drug Allergy Interest Group: Skin test concentrations for systemically administered drugs—An ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013; 68:702–12
9. Fisher MM, Merefield 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. Australian and New Zealand Anaesthetic Allergy Group (ANZAAG): ANZAAG Anaphylaxis Management Guidelines (2013–2015). Available at: http://www.anzaag.com/Mgmt%20Resources.aspx. Accessed May 16, 2015
12. Dewachter P, Castells MC, Hepner DL, Mouton-Faivre C: Perioperative management of patients with mastocytosis. Anesthesiology 2014; 120:753–9
13. Adam B, Van Loon J: Introduction. Repositioning risk: The challenge for social theory, The Risk Society and Beyond: Critical Issues for Social Theory. Edited by Adam B, Beck U, Van Loon J. Thousand Oaks, Sage, 2000, pp 1–32
14. Lienhart A, Auroy Y, Péquignot F, Benhamou D, Warszawski J, Bovet M, Jougla E: Survey of anesthesia-related mortality in France. Anesthesiology 2006; 105:1087–97
15. Auroy Y, Benhamou D, Péquignot F, Jougla E, Lienhart A: [Survey of anaesthesia-related mortality in France: The role of aspiration of gastric contents]. Ann Fr Anesth Reanim 2009; 28:200–5

(Accepted for publication May 14, 2015.)