Sugammadex Anaphylaxis: Mechanisms, Diagnosis, and Incidence

Louise Savic, M.B., B.S., Jonathan A. Silversides, M.B., B.Ch., B.A.O.(Hon), Ph.D.,
Kate Leslie, M.B.B.S., M.Epid., M.Hlth.Serv.Mt., M.D., Hon.D.Med.Sci.

Global use of sugammadex, a novel encapsulating agent for reversal of aminosteroid-induced neuromuscular blockade, has hitherto been limited by lack of regulatory approval, limited supply, institutional policies, and self-imposed restrictions.[1] Since the expiry of patent protections in many countries, generic preparations have entered the market, facilitating local supplies at lower cost. Even in the United States, where patent protection has been extended until at least January 2026, sugammadex sales are growing.[2] The aims of this clinical focus review are to (1) discuss the risks and benefits of sugammadex and neostigmine for reversal of neuromuscular blockade and (2) review the literature about sugammadex, neostigmine, and neuromuscular-blocking drug (NMBD) allergy, because reversal agents are usually administered to patients who have received a NMBD, and NMBDs (in particular rocuronium) are a leading cause of anesthetic-related anaphylaxis worldwide.[3]

Reversal of Neuromuscular Blockade

Traditionally, reversal is achieved with an anticholinesterase (*e.g.*, neostigmine) combined with an antimuscarinic agent (*e.g.*, glycopyrrolate).[4] The undesired effects of anticholinesterase reversal include inadequately opposed cholinergic effect (*e.g.*, bradycardia,[5] increased intestinal motility,[6] and postoperative nausea and vomiting[7]) and excessive antimuscarinic effect (*e.g.*, tachycardia and urinary retention[4]). In addition, there are largely theoretical concerns that neostigmine may cause muscle weakness if administered to patients who have fully recovered from neuromuscular blockade.[8] Sugammadex is a more recent addition to the reversal armamentarium for aminosteroid NMBDs. The undesired effects of sugammadex include bradycardia, asystole, and anaphylaxis.[4] In addition, cases of laryngospasm have been reported.[9]

Sugammadex offers proven and potential advantages over neostigmine, which are the foundations for enthusiasm about its use. In a meta-analysis of randomized trials, sugammadex reversed moderate (train-of-four count = 2) and deep (posttetanic count = 1) rocuronium-induced neuromuscular blockade more rapidly and more reliably than neostigmine, resulting in lower incidences of residual neuromuscular blockade and clinical signs of weakness in the postanesthesia care unit.[7] Differences after reversal of light blockade (train-of-four count = 4) are less clinically significant.[10] Notably, residual neuromuscular blockade is still reported after sugammadex administration, likely due to inadequate dosing and failure to confirm complete reversal with quantitative neuromuscular monitoring.[11]

As a result of superior reversal of neuromuscular blockade, sugammadex use is associated with a lower incidence of early adverse respiratory events, such as desaturation and the need for oxygen supplementation in the postanesthesia care unit.[7] Large cohort studies[12,13] and small randomized trials[14] provide preliminary evidence that sugammadex reduces the incidence of longer-term pulmonary complications, such as atelectasis, pneumonia, acute respiratory distress syndrome, and aspiration pneumonitis, potentially improving patient-centered outcomes such as hospital length of stay, readmission, and mortality. To date, however, definitive evidence about longer-term complications is lacking, and large randomized clinical effectiveness trials are ongoing (UK Clinical Study Registry ISRCTN15109717 and Australian and New Zealand Clinical Trial Registry ACTRN12623000394640).

Using sugammadex avoids most of the aforementioned neostigmine- and glycopyrrolate-related side effects. However, bradycardia is a recognized side effect of both neostigmine and sugammadex.[4] In the case of neostigmine, bradycardia results from an inadequately antagonized cholinergic effect. In the

Submitted for publication November 7, 2024. Accepted for publication February 25, 2025.

Louise Savic, M.B., B.S., M.R.C.P.: Department of Anaesthesia, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Jonathan A. Silversides, M.B., B.CH., B.A.O. (Hons), Ph.D., M.R.C.P.: Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom; Department of Anaesthesia and Critical Care, Belfast Health and Social Care Trust, Belfast, United Kingdom.

Kate Leslie, M.B.B.S., M.Epid., M.Hlth.Serv.Mt., M.D., Hon.D.Med.Sci.: Department of Critical Care, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia; Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Victoria, Australia.

 ANESTHESIOLOGY 2025; XXX:XX–XX. DOI: 10.1097/ALN.0000000000005431

Abbreviations: ASA, American Society of Anesthesiologists; **ESAIC**, European Society of Anaesthesiology and Intensive Care; **MRGPRX2**, Mas-related G protein receptor X2; **NAP6**, 6th National Audit Project; **NMBD**, neuromuscular blocking drug

<zdoi;10.1097/ALN.0000000000005431>

case of sugammadex, the cause is unclear. In both cases, bradycardia is usually mild and transient, but profound severe bradycardia and asystole have been reported with sugammadex administration, usually after higher doses.[15] Meta-analyses suggest that the incidence of bradycardia is lower with sugammadex than with neostigmine,[7] but adverse event reports to the U.S. Food and Drug Administration (Silver Spring, Maryland) suggest the opposite.[5] The latter may reflect a reporting bias, given that bradycardia is such a well-recognized and understood side effect of neostigmine. Anaphylaxis is rarely reported with neostigmine (a systematic review revealed only eight reported cases[16]), but there is considerable concern about its incidence in association with sugammadex (see 'Incidence of NMBD and Sugammadex Allergy').[17]

Recent guidelines support the preferential use of sugammadex over neostigmine for reversal of aminosteroid NMBDs. The American Society of Anesthesiologists (ASA) strongly recommends sugammadex over neostigmine at all but minimal depths of rocuronium- and vecuronium-induced neuromuscular blockade, citing a moderate level of evidence for a shorter time to a train-of-four ratio greater than 0.9 and a lower incidence of residual neuromuscular blockade.[18] A similar recommendation was made by the European Society of Anaesthesiology and Intensive Care (ESAIC).[19] The ASA stated that their strength-of-evidence ratings did not support differences in the risk of anaphylaxis between neostigmine/glycopyrrolate and sugammadex,[18] and the ESAIC stated, "It is certainly difficult to ascertain the true incidence of any rare adverse event; however, the risk of anaphylaxis alone should not be an over-riding factor in the choice of reversal agent."[19]

Allergy, Hypersensitivity, and Anaphylaxis

Before we proceed further, we need to define what is meant by "allergy," "hypersensitivity" and "anaphylaxis." Although these terms are used interchangeably in the literature, they do not mean precisely the same thing (table 1). Various international statements define and delineate these terms, albeit with inconsistent nomenclature.[20–22]

Allergy describes a reaction to an exogenous substance (allergen) that is driven by the immune system.[20–22] *Hypersensitivity* is generally used to describe reactions that clinically resemble allergy, causing reproducible symptoms on exposure to a substance at a dose that is tolerated by normal subjects.[20–22] Hypersensitivity reactions include those that are immune-mediated, as well as those with no underpinning immune mechanism. *Anaphylaxis* simply describes hypersensitivity reactions that are severe or life-threatening.[20–22] The term is agnostic to the underlying mechanism(s), and anaphylaxis can be either allergic or nonallergic. Irrespective of the mechanism, the result is massive systemic release of inflammatory mediators leading to the clinical syndrome of anaphylaxis.

In the context of perioperative reactions, allergy refers to immunoglobulin E–mediated reactions.[22] In this pathway, exposure to the allergen results in a clinically silent sensitization phase, during which antiallergen immunoglobulin E antibodies are produced. These coat the surface of mast cells and basophils, thereby "priming" them. On re-exposure, the cells are activated to release the contents of preformed granules containing effector mediators such as histamine, leukotrienes, and prostaglandins. This results in the clinical symptoms and signs of allergy. The thresholds at which mast cells are activated to degranulate occurs varies between, and within, individuals. In addition to immunoglobulin E–mediated reactions, allergic mechanisms involving immunoglobulin G antibodies have been suggested for some drugs.[22,23]

However, hypersensitivity reactions in the perioperative setting can also be caused by nonallergic mechanisms.[22] Such mechanisms are thought to include direct activation of cell membrane receptors such as the Mas-related G protein receptor X2 (MRGPRX2), expressed constitutively on mast cells, and inducibly on basophils.[24] The evidence for this is mostly limited to animal and *in vitro* models, but such pathways provide a plausible explanation for the observation that patients

Table 1. Allergic and Nonallergic Hypersensitivity and Anaphylaxis in the Perioperative Setting

Term	Definition	Mechanism(s)	Previous Allergen Exposure
Allergic hypersensitivity	Specific pathophysiologic process involving the adaptive immune system	IgE-mediated* IgG-mediated (limited data in humans)	Yes
Nonallergic hypersensitivity	Idiosyncratic drug reaction with identical clinical features to allergy, mediated by a variety of mechanisms	Complement-mediated through complement components C3a and C5a MRGPRX2-mediated Cyclo-oxygenase-1 inhibition Kinin-kallikrein system Unknown mechanisms	Not necessarily
Anaphylaxis	Any hypersensitivity reaction that is severe or life-threatening	Allergic or nonallergic	Not necessarily

*This definition does not take into account other allergic mechanisms that are not typically seen in the perioperative setting, including type II cytotoxic and type III immune-complex reactions (both antibody- mediated) or cell-mediated, delayed hypersensitivity reactions.

IgE, immunoglobulin E; IgG, immunoglobulin G; MRGPRX2, Mas-related G protein receptor X2.

can react to a drug on first exposure, without a previous sensitizing event. This is particularly relevant for NMBDs, as discussed below. Hypersensitivity reactions through complement activation, cyclo-oxygenase-1 inhibition, or disruption of the kinin-kallikrein system can also occur.

It is outside the scope of this review to discuss the clinical features of anaphylaxis. However, it is important to point out that sugammadex anaphylaxis presents in a similar way to other anesthetic-related events, except that it occurs at the end of the case. Continued routine monitoring and a high index of suspicion are required for rapid diagnosis and treatment.

Mechanisms of Hypersensitivity to NMBDs and Sugammadex

Sugammadex administration follows neuromuscular blockade, so NMBD hypersensitivity is germane to this discussion. The mechanisms underpinning reactions to NMBDs and sugammadex have not been fully elucidated. The observation that patients can react on first exposure to NMBDs suggests that allergic sensitization might occur through exposure to a shared allergenic epitope (*i.e.*, a region on the surface of an antigen that is recognized by the immune system) in drugs or compounds found outside healthcare settings. A shared allergenic epitope is the basis of the "pholcodine hypothesis," which postulates that the substituted ammonium ion in pholcodine sensitizes patients to the substituted ammonium ion in NMBDs.[25–28] The evidence for this is largely circumstantial, linking previous pholcodine use to a possible increased risk of suspected NMBD anaphylaxis.[29] A shared allergenic epitope is also the basis for morphine-specific immunoglobulin E measurement used as a surrogate marker for NMBD allergy.[30,31] However, this has been abandoned in some centers as a testing modality, because of the poor correlation with clinical NMBD sensitivity.[32] Interestingly, the presence of pholcodine-specific immunoglobulin E antibodies does not result in clinical reactivity to pholcodine.

An alternative hypothesis is that hypersensitivity to NMBDs does not result from acquired immunity but instead may be caused by one of the innate immune pathways described above. This might better explain reactions that occur on first exposure.[22,24] The role of MRGPRX2 and other mast cell receptors in perioperative drug hypersensitivity is an area of active research.[24]

Little is known about the mechanism of sugammadex hypersensitivity. Concerns were initially raised about possible environmental sensitization through ingestion of γ-cyclodextrins, found in emulsifiers and color enhancers in food, which might account for the occurrence of reactions on first exposure. There are no robust data available to support this hypothesis at present. However, as described ('Allergy, Hypersensitivity, and Anaphylaxis'), these reactions might be better explained by activation of innate pathways such as the MRGPRX2 receptor.[33] An accumulating body of evidence suggests that as usage increases and patients are re-exposed to the drug through repeat surgeries, the likelihood of sugammadex hypersensitivity increases. This would indicate that a learned immune response, mediated through specific anti-drug antibodies, is at least one plausible mechanism. More research is needed into both NMBD and sugammadex hypersensitivity to elucidate these pathways.

Testing for NMBD and Sugammadex Allergy

Testing after a presumed sugammadex anaphylaxis will include testing for both sugammadex and NMBD allergy. There is currently no *in vitro* test that can confirm or exclude allergy to an NMBD, sugammadex, or any other drug with 100% sensitivity or specificity.[34] *In vivo* tests, including skin prick and intradermal tests, have poorly defined sensitivity and specificity. This is especially the case for NMBDs, where data to validate these tests cannot be obtained using challenge testing as the gold standard. In the context of a high pretest probability of genuine hypersensitivity, a positive skin test is accepted to be confirmatory. However, the negative predictive value in this context is not known. Conversely, with a low pretest probability, the negative predictive value is thought to be good, but the positive predictive value remains unknown. Robust data on cross-reactivity between NMBDs are limited, for the same reasons, and are not yet available for sugammadex and emerging encapsulating reversal agents.

In vitro tests include quantification of specific immunoglobulin E antidrug antibodies, using enzyme-linked immunosorbent assays and other techniques.[34–36] However, while the presence of a specific immunoglobulin E antibody to a drug indicates sensitization, a positive result may not predict clinical allergy.[37] Conversely, the failure to detect a specific immunoglobulin E antibody does not exclude allergy.[37] Specific immunoglobulin E assays are not yet available for clinical use for most perioperative drugs, including the nondepolarizing NMBDs and sugammadex. An additional complication with sugammadex testing is that some case reports have demonstrated positive skin testing only when a rocuronium–sugammadex mixture is used, with testing for either drug in isolation being negative.[38] It has been suggested that the binding of sugammadex to rocuronium results in a conformational changes to the carboxyethyl side chains attached at the primary rim of sugammadex, which in effect creates a novel antigen that is then recognized by the immunoglobulin E antibody.[38] Nevertheless, other patients have tested negative to the rocuronium–sugammadex complex while testing positive to sugammadex alone, and it is possible that these two allergies may both exist.[39]

Novel diagnostic tools, including the basophil activation test and mast cell activation test, provide a functional assay of clinical reactivity to a drug irrespective of underlying mechanism. However, these assays are unvalidated, exist predominantly in the research domain, and are unavailable in most allergy clinics.[40]

Incidence of NMBD and Sugammadex Allergy

The incidence of perioperative hypersensitivity reactions is hard to define. First, potential hypersensitivity reactions are widely accepted to be underreported. For example, the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists reported a hypersensitivity reaction incidence of 1:10,000 (0.01%), estimating underreporting of up to 70%.[41] A prospective study of 4,595 anesthetics in the United Kingdom found that 13 patients (1:353; 0.28%) patients suffered an adverse perioperative event that met criteria for referral to allergy clinic. Of these 13 patients, 3 had confirmed allergy on testing (1:2,000; 0.05%).[42] Underreporting can result from misattribution of the reaction to other causes, failure to refer for testing, or inadequate access to allergy services. Second, variations in rates of diagnosis, case definition, and the methods for determining numerator and denominator data prevent meaningful comparison between studies. Guidelines on concentrations to use for skin testing change over time and differ between countries, with different thresholds for assigning test results positive or negative.[37] Many centers rely heavily on *in vitro* tests, which may be unavailable elsewhere, or considered insufficiently validated to use for diagnosis. Last, there has been limited collaboration within and between countries to allow for meta-analysis of pooled data. All discussion about incidence must therefore be approached with a high degree of caution.

In the context of this review, the incidences of both NMBD and sugammadex allergy are relevant. Existing literature suggests that the incidence of NMBD allergy varies widely across geographical regions, with France, Australia, New Zealand, the United Kingdom, and Spain among the countries with highest incidence, at 184 to 251 cases per million NMBD exposures (0.018%).[3] In contrast, a study in the United States reported lower incidences (*e.g.*, two reported cases among 1,150,000 anesthetics at a single center [0.0002%]).[43] In terms of the relative risk of individual NMBDs, the NAP6 report concluded that the likelihood of allergy to atracurium and rocuronium was broadly similar,[41] in contrast to earlier reports from other countries suggesting that rocuronium might have a greater propensity to cause allergy.[44,45]

The incidence of sugammadex allergy is even harder to determine. Postmarketing surveillance data published in 2016 suggested an incidence of 1:42,000 (0.0024%), with 273 cases reported among approximately 11.3 million exposures.[46] However, in Japan, where rocuronium is the NMDB of choice and sugammadex has been used as a first-line reversal agent since 2010, much higher incidences have been determined: 1:2,500 (0.039%) in a single-center study in 2018[47] and 1:5,000 (0.02%) in a multicenter study in 2020.[17] Some of these differences might be accounted for by variation in case classification. In the 2018 study, the diagnosis was made largely in the absence of confirmatory testing, and the true denominator for use of sugammadex was unknown, while in the 2020 study, a more robust assessment of both these factors was provided.[17,47] In NAP6 (2018), an incidence of 0.0016% was reported, with one case confirmed among an estimated 64,000 administrations.[41] At this time, sugammadex was not freely available in the United Kingdom, and usage was limited to particular clinical settings. Based on the 2020 study[17] and NAP6,[41] it seems that the rocuronium–sugammadex combination (19.23 cases per 100,000 patients) is associated with more anaphylaxis than atracurium–neostigmine (4.15 cases per 100,000 patients).[48]

No national level data have been reported since 2020, although a few reviews and case reports have been published. A systematic review of sugammadex allergy published in 2021 reported on 33 cases in the worldwide literature, with Japan contributing a high proportion of included cases.[49] Of these, only 19 had positive skin testing, with a further two diagnosed on the basis of serum-specific immunoglobulin E alone. The remaining patients underwent no testing at all or had negative tests. The diagnosis can therefore only be made with confidence in 19 patients. In a recent study, investigators in Australia reported hypersensitivity to sugammadex diagnosed by positive intradermal or skin prick testing at six perioperative allergy clinics in two states over a 13-yr period.[50] A total of 30 cases were included (15 life-threatening and 15 non–life-threatening). Using population statistics for the denominator, the estimated incidence of sugammadex hypersensitivity was 0.004% (95% CI, 0.002 to 0.008%) or 1:25,000. This appeared to be a lower incidence that previously observed.[3] Overall, the incidence appears to be low, and outside of Japan, there is no clear signal as yet that sugammadex hypersensitivity has become a significant problem.

Research Agenda and Conclusions

Robust international data about NMBD and sugammadex use, clinical reports of hypersensitivity and confirmed cases of allergy are required. It will be particularly important to engage and support resource-limited settings in which sugammadex is introduced, because these institutions may not have the infrastructure to undertake clinical testing nor systematically collect data. Further research is required to identify underlying mechanisms in hypersensitivity to NMBD, sugammadex, and the NMDB–sugammadex complex. Finally, the development of novel diagnostic tests and validation of existing tests is vital.

Sugammadex offers indisputable benefits over neostigmine, rapidly and effectively reversing moderate to deep neuromuscular blockade and dramatically reducing the risk of residual neuromuscular blockade, especially if dosing and recovery are guided by quantitative neuromuscular monitoring. Residual neuromuscular blockade is common (greater than 5%) and represents a known major risk factor for significant adverse events in the postanesthesia care unit and beyond. Sugammadex anaphylaxis is rare (less than

0.02%) but also may be life-threatening, and the compounding risk associated with NMBD allergy also needs to be considered. However, even with the increasing use and reuse of sugammadex worldwide, there is no evidence for a surge of NMBD–sugammadex–related anaphylaxis.

Research Support

Supported by United Kingdom National Institute (London, England) for Health Research Health Technology Assessment grant No. NIHR133056 and Australian Medical Research Future Fund (Canberra, Australia) grant No. APP2022850.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Prof. Leslie: Royal Melbourne Hospital, 300 Grattan Street, Parkville, Victoria 3052, Australia. kate.leslie@mh.org.au

References

1. O'Reilly-Shah VN, Wolf FA, Jabaley CS, Lynde GC: Using a worldwide in-app survey to explore sugammadex usage patterns: A prospective observational study. Br J Anaesth 2017; 119:333–5
2. Merck & Co, Inc.: Merck announces fourth-quarter and full-year 2023 financial results. Available at: https://www.merck.com/news/merck-announces-fourth-quarter-and-full-year-2023-financial-results/. Accessed October 30, 2024.
3. Mertes PM, Ebo DG, Garcez T, et al.: Comparative epidemiology of suspected perioperative hypersensitivity reactions. Br J Anaesth 2019; 123:e16–28
4. Brull SJ, Meistelman C, Nemes R, de Boer HD, Thilen S, Eriksson LI: Pharmacology of neuromuscular blocking drugs and antagonists (reversal agents), Miller's Anesthesia. Edited by M Gropper, Philadelphia, Elsevier, 2024, pp. 674–741
5. Johnson KB, Chacin R: Clarifying the grey space of sugammadex induced bradycardia. Curr Opin Anaesthesiol 2023; 36:422–7
6. Vaghiri S, Prassas D, Krieg S, Knoefel WT, Krieg A: The postoperative effect of sugammadex versus acetylcholinesterase inhibitors in colorectal surgery: An updated meta-analysis. J Clin Med 2023; 12:3235
7. Hristovska AM, Duch P, Allingstrup M, Afshari A: Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev 2017; 8:CD012763
8. Naguib M, Kopman AF: Neostigmine-induced weakness: What are the facts? Anaesthesia 2018; 73:1055–7
9. Greenaway S, Shah S, Dancey M: Sugammadex and laryngospasm. Anaesthesia 2017; 72:412–3
10. Pongrácz A, Szatmári S, Nemes R, Fülesdi B, Tassonyi E: Reversal of neuromuscular blockade with sugammadex at the reappearance of four twitches to train-of-four stimulation. Anesthesiology 2013; 119:36–42
11. Todd MM, Kopman AF: Sugammadex is not a silver bullet: Caveats regarding unmonitored reversal. Anesthesiology 2023; 139:1–3
12. Kirmeier E, Eriksson LI, Lewald H, et al.; POPULAR Contributors: Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): A multicentre, prospective observational study. Lancet Respir Med 2019; 7:129–40
13. Kheterpal S, Vaughn MT, Dubovoy TZ, et al.: Sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER): A multicenter matched cohort analysis. Anesthesiology 2020; 132:1371–81
14. Olesnicky BL, Farrell C, Clare P, Wen S, Leslie K, Delaney A: The effect of sugammadex on patient morbidity and quality of recovery after general anaesthesia: A systematic review and meta-analysis. Br J Anaesth 2024; 132:107–15
15. Bhavani SS: Severe bradycardia and asystole after sugammadex. Br J Anaesth 2018; 121:95–6
16. de Boer HD, Hunter JM: Sugammadex or neostigmine: Should potential anaphylaxis be the overriding factor in the choice of a reversal drug? Comment on Br J Anaesth 2020; 124:154–63. Br J Anaesth 2020; 125:e220–1
17. Orihara M, Takazawa T, Horiuchi T, et al.: Comparison of incidence of anaphylaxis between sugammadex and neostigmine: A retrospective multicentre observational study. Br J Anaesth 2020; 124:154–63
18. Thilen SR, Weigel WA, Todd MM, et al.: 2023 American Society of Anesthesiologists practice guidelines for monitoring and antagonism of neuromuscular blockade: A report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade. Anesthesiology 2023; 138:13–41
19. Fuchs-Buder T, Romero CS, Lewald H, et al.: Perioperative management of neuromuscular blockade: A guideline from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol 2023; 40:82–94
20. Jutel M, Agache I, Zemelka-Wiacek M, et al.: Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy 2023; 78:2851–74
21. Tanno LK, Calderon MA, Smith HE, Sanchez-Borges M, Sheikh A, Demoly P; Joint Allergy Academies: Dissemination of definitions and concepts of allergic and hypersensitivity conditions. World Allergy Organ J 2016; 9:24
22. Ebo DG, Clarke RC, Mertes PM, Platt PR, Sabato V, Sadleir PHM: Molecular mechanisms and

pathophysiology of perioperative hypersensitivity and anaphylaxis: A narrative review. Br J Anaesth 2019; 123:e38–49
23. Bruhns P, Chollet-Martin S: Mechanisms of human drug-induced anaphylaxis. J Allergy Clin Immunol 2021; 147:1133–42
24. Elst J, van der Poorten MM, Faber MA, et al.: Mast cell activation test in chlorhexidine allergy: A proof of concept. Br J Anaesth 2020; 125:970–5
25. European Medicines Agency: Pholcodine medicines withdrawn from EU market. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/pholcodine-containing-medicinal-products. Accessed October 30, 2024.
26. Medicines and Healthcare Products Regulatory Agency: Safety withdrawal of pholcodine-containing cough and cold medicines. Available at: https://www.gov.uk/government/news/safety-withdrawal-of-pholcodine-containing-cough-and-cold-medicines. Accessed October 30, 2024.
27. Florvaag E, Johansson SG: The pholcodine case. Cough medicines, IgE-sensitization, and anaphylaxis: A devious connection. World Allergy Organ J 2012; 5:73–8
28. Mertes PM, Petitpain N, Tacquard C, et al.: Pholcodine exposure increases the risk of perioperative anaphylaxis to neuromuscular blocking agents: The ALPHO case-control study. Br J Anaesth 2023; 131:150–8
29. Savic L, Hopkins PM: Pholcodine and allergy to neuromuscular blocking agents: Where are we and how did we get here? Br J Anaesth 2024; 132:457–60
30. Baldo BA, Fisher MM: Substituted ammonium ions as allergenic determinants in drug allergy. Nature 1983; 306:262–4
31. Chow KL, Patchett K, Reeves G, de Malmanche T, Gillies D, Boyle M: Morphine-specific IgE testing in the assessment of neuromuscular blocking agent allergy: A single centre experience. Br J Anaesth 2024; 132:193–5
32. Ebo DG, Vlaeminck N, van der Poorten ML, et al.: Morphine-specific IgE testing in the diagnosis of neuromuscular blocking agent allergy: Proper use and interpretation. Br J Anaesth 2024; 133:915–7
33. de Kam PJ, Nolte H, Good S, et al.: Sugammadex hypersensitivity and underlying mechanisms: A randomised study of healthy non-anaesthetised volunteers. Br J Anaesth 2018; 121:758–67
34. Volcheck GW, Melchiors BB, Farooque S, et al.: Perioperative hypersensitivity evaluation and management: A practical approach. J Allergy Clin Immunol Pract 2023; 11:382–92
35. Mayorga C, Perez-Inestrosa E, Molina N, Montañez MI: Development of nanostructures in the diagnosis of drug hypersensitivity reactions. Curr Opin Allergy Clin Immunol 2016; 16:300–7
36. Garvey LH, Savic LC: Drug provocation testing: Risk stratification is key. Curr Opin Allergy Clin Immunol 2019; 19:266–71
37. 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
38. Ebo DG, Baldo BA, Van Gasse AL, et al.: Anaphylaxis to sugammadex–rocuronium inclusion complex: An IgE-mediated reaction due to allergenic changes at the sugammadex primary rim. J Allergy Clin Immunol Pract 2020; 8:1410–5.e3
39. Sadleir PH, Russell T, Clarke RC, Maycock E, Platt PR: Intraoperative anaphylaxis to sugammadex and a protocol for intradermal skin testing. Anaesth Intensive Care 2014; 42:93–6
40. 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
41. 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
42. Savic LC, Kaura V, Yusaf M, et al.; Anaesthetic Audit and Research Matrix of Yorkshire: Incidence of suspected perioperative anaphylaxis: A multicenter snapshot study. J Allergy Clin Immunol Pract 2015; 3:454–5.e1
43. Gurrieri C, Weingarten TN, Martin DP, et al.: Allergic reactions during anesthesia at a large United States referral center. Anesth Analg 2011; 113:1202–12
44. 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
45. Rose M, Fisher M: Rocuronium: High risk for anaphylaxis? Br J Anaesth 2001; 86:678–82
46. Murphy G: The development and regulatory history of sugammadex in the United States. APSF Newsl 2016; 30:53–4
47. Miyazaki Y, Sunaga H, Kida K, et al.: Incidence of anaphylaxis associated with sugammadex. Anesth Analg 2018; 126:1505–8
48. Savic L, Savic S, Hopkins PM: Anaphylaxis to sugammadex: Should we be concerned by the Japanese experience? Br J Anaesth 2020; 124:370–2
49. Arslan B, Sahin T, Ozdogan H: Sugammadex and anaphylaxis: An analysis of 33 published cases. J Anaesthesiol Clin Pharmacol 2021; 37:153–9
50. Crimmins D, Crilly H, van Nieuwenhuysen C, et al.: Sugammadex hypersensitivity: A multicentre retrospective analysis of a large Australian cohort. Br J Anaesth 2024; 134:72–9