



Letter

Sugammadex

An emerging trigger of intraoperative anaphylaxis

Neuromuscular blocking agents (NMBAs) and antibiotics are the most common triggers of intraoperative anaphylaxis. Sugammadex, a modified γ -cyclodextrin, rapidly reverses aminosteroid NMBAs (rocuronium and vecuronium) and acts 3 to 8 times faster than neostigmine.¹ It has a good safety profile and has been licensed in more than 70 countries. However, the US Food and Drug Administration (FDA) approved it only recently in December 2015.² Anaphylaxis to this drug occurs rarely, estimated at 29 per 1,000,000 population, usually at the end of anesthesia when sugammadex is used for NMBA reversal.³ Sporadic cases have been reported, mainly from the Far East, where sugammadex is used more commonly than in Europe or North America.^{1,3}

We report the first 3 British cases of sugammadex anaphylaxis referred to our centers between February and March 2016. Induction and maintenance of anesthesia were uneventful in all cases. All patients developed severe anaphylaxis with profound hypotension, tachycardia, and generalized urticaria within 5 minutes of administration of 100 to 400 mg of sugammadex (100 mg/mL; Bridion; MSD Ltd, London, United Kingdom). No other drugs were given around that time. Detailed clinical features and the results of investigations are given in Table 1. The interval between the administration of general anesthetics and other drugs and onset of hypersensitivity reaction was too prolonged to consider them likely culprits. No nonsteroidal anti-inflammatory drugs, opioids, antibiotics, or antiemetics were used toward the end of surgery. Moreover, all drugs, except sugammadex, tested negative on skin prick tests (SPTs) and intradermal tests (IDTs), including chlorhexidine and latex. All patients provided written informed consent for publication.

In our case series, the chronology and immediacy of reactions, positive SPT and IDT results to sugammadex, negative SPT and IDT results to all other agents, and increased acute serum tryptase levels make sugammadex the most likely culprit for intraoperative anaphylaxis. A recent systematic review included 15 patients with sugammadex hypersensitivity. Only 11 underwent either SPTs or IDTs; 1 had a negative result.⁴ Although there are no standardized protocols for the investigation of sugammadex-induced anaphylaxis, certain elements are crucial: detailed history, short interval between administration of sugammadex and onset of reaction, skin tests, and serum tryptase measurements. There are no commercial sugammadex specific IgE assays, and the basophil activation test has been used only experimentally.⁴ Some authors propose omitting SPTs and proceeding straight to IDTs.⁵ Because fatal anaphylaxis to IDTs with drugs has been reported, we propose that SPTs should always be performed first, followed by IDTs if SPT results are negative.⁶ Optimal concentration of sugammadex for skin testing has not been validated in large studies. However, SPTs with

undiluted (100 mg/mL) and IDTs with a 1:100 and 1:1,000 dilution of the standard 100 mg/mL of solution appeared nonirritant in previous studies.^{1,3–5} Since the 2014 review on sugammadex anaphylaxis, at least 3 articles on this topic have been published.^{1,4,7,8} These authors undertook SPTs and/or IDTs or no skin tests at all. Acute tryptase was not measured.^{1,7,8} Therefore, in the absence of urticaria, angioedema, or bronchospasm, other causes of intraoperative shock, such as hypovolemia or sepsis, cannot be reliably excluded, and the assumption of anaphylaxis might be questionable.

Cyclodextrins are made up of 6, 7, or 8 dextrose units (α -, β -, and γ -cyclodextrins, respectively). Sugammadex is a cyclodextrin with a lipophilic core and hydrophilic periphery. It is used to reverse neuromuscular blockade by encapsulating NMBAs and displacing them from their receptors.^{1,3} Cyclodextrins are also used to improve water solubility and bioavailability of medicines by interacting with hydrophobic drug molecules to form inclusion complexes (eg, β -cyclodextrin in cetirizine tablets, β -cyclodextrin derivatives in intravenous voriconazole, and γ -cyclodextrin in minoxidil solution).^{1,9} Interestingly, they are not included in the European Commission's guideline on excipients labeling of medicinal products. In food industry, they act as emulsifiers (α -cyclodextrins), color enhancers (β -cyclodextrin with carotenoids), and emulsion stabilizers (γ -cyclodextrin).^{9,10} It has been estimated that an average person consumes approximately 4 g of γ -cyclodextrin per day.¹⁰ It is possible that orally ingested cyclodextrins cause sensitization and predispose patients to sugammadex hypersensitivity, which might explain why all patients in our case series developed anaphylaxis on first exposure, similarly to some cases reported previously.⁴ However, none of our patients reported adverse reactions to food. Their regular medications did not contain cyclodextrins. Preexisting antibodies are known to cause anaphylaxis on first exposure to drugs (eg, oral sensitization attributable to cough suppressant pholcodine predisposing patients to anaphylaxis to NMBA [pholcodine hypothesis]).¹¹

Data are limited on the allergenic epitopes of sugammadex, a modified γ -cyclodextrin that contains 8 thiopropionate side chains. Hotta et al¹ performed SPTs or IDTs (depending on water solubility and irritancy) with α -, β -, and γ -cyclodextrin, methyl 3-mercaptopropionate, and ethyl 3-methylthiopropionate, the last 2 found in thiopropionate, the side chains of sugammadex.¹ Only the γ -cyclodextrin IDT result was positive. This 8-dextrose unit might be responsible for hypersensitivity reactions. On the basis of this limited evidence, cross-reactivity with other cyclodextrins seems unlikely.¹

Sugammadex is an emerging trigger for perioperative anaphylaxis. With the recent FDA approval in the United States, an increase in the number of cases of suspected hypersensitivity can be

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Table 1
Three Patients With Sugammadex Anaphylaxis: Clinical Features and Investigations

Age, y/sex	Procedure and dose of sugammadex	Reaction	Treatment	SPT result (1:1) size, mm	IDT result increase in size (from original bleb), mm	Serum tryptase, $\mu\text{g/L}$		First exposure
						Acute	Baseline	
50/M	Ureteric stent replacement; 200 mg	Hypotension (SBP, 45 mm Hg), tachycardia (heart rate, 106/min), desaturation (81%), generalized urticaria	A, H, C	5	5	81	9	Yes
62/M	Gingival lesion removal; 400 mg	Hypotension (SBP, 60 mm Hg), diaphoresis, unresponsiveness (GCS score, 3/15)	A, H, C	7	4	141	7	Yes
63/M	Sleeve gastrectomy; 100 mg	Hypotension (SBP, 66 mm Hg), tachycardia (heart rate, 118/min), desaturation (50%), generalized urticaria	A, H, C	0	8	36	10	Yes

Abbreviations: A, adrenaline; C, chlorphenamine; H, hydrocortisone; GCS, Glasgow Coma Scale; IDT, intradermal test; SBP, systolic blood pressure; SPT, skin prick test.

expected. We propose an algorithm for investigations of such hypersensitivity reactions that encompasses detailed history, anesthetic medical record review, measurements of acute and baseline serum tryptase levels and SPT with stock solution of sugammadex (100 mg/mL) before proceeding to IDTs with 1:100 and 1:1,000 dilutions of the standard solution. The optimal concentration for skin testing should be validated in a larger cohort of allergic and nonallergic individuals. Further studies are required to identify the allergenic epitope(s) of sugammadex and the existence of cross-reactivity among various cyclodextrins. A potential link between oral sensitization to cyclodextrins and risk of anaphylaxis to intravenous or oral medication containing cyclodextrins warrants further studies. It is open for discussion whether avoidance of all cyclodextrins in food and medicines should be recommended to patients with confirmed sugammadex allergy and whether cyclodextrins should appear on the list of excipients in the medicinal products. Finally, the anesthetic and allergy/immunology communities should be educated about the risk of anaphylaxis after NMBA reversal because of this newly approved drug.

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