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Anaphylaxis (M Sanchez-Borges, Section Editor)

Perioperative Reactions to Sugammadex

Brian A. Baldo, PhD

Address
[1]Molecular Immunology Unit, Kolling Institute of Medical Research, Royal North Shore, Hospital of Sydney, Sydney, NSW, Australia
Department of Medicine, University of Sydney, Sydney, NSW, Australia
Email: babaldo@iinet.net.au

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Brian A. Baldo is retired. The positions and affiliations listed are those prior to his retirement

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Abstract

Purpose of the review The γ-cyclodextrin sugammadex, chemically modified to encapsulate the steroidal muscle relaxant rocuronium, was introduced into anesthesia as the first selective relaxant binding agent to reverse neuromuscular blockade. In the face of sugammadex's alleged propensity to cause anaphylaxis, the agent was finally approved by the FDA in 2015. With its steadily increasing usage, it has become apparent that there is a small but concerning incidence of perioperative anaphylaxis to sugammadex and some reactions that are anaphylactic like but where diagnosis has not been definitive. The purpose here is to examine the symptoms of the induced reactions, successful treatments undertaken, diagnostic conclusions reached, and the terminology applied to the reactions studied.

Recent findings Following relatively large numbers of early reports of anaphylaxis to sugammadex in Japan (where it was approved in 2010), accumulated data and evidence for the drug's involvement in provoking reactions has been assembled (from Japan and elsewhere) and analyzed from 33 case reports and other relevant publications. A feature of the diagnostic conclusions is the varied terminology and nomenclature ascribed to the observed reactions with up to nine different diagnostic descriptions used. Although anaphylaxis is the most commonly applied designation, compelling evidence for an immune basis for many of the reported reactions is lacking. In accord with early predictions, the sugammadex-rocuronium inclusion complex has been shown to be allergenic with IgE/FcεRI-dependent anaphylaxis occurring in some patients. The basis of the immune recognition appears to be a shape alteration involving the thiocarboxyethyl sodium side chains attached at the primary ring of the host sugammadex molecule creating a new allergenic determinant.

Summary Although still relatively rare, severe, even life threatening, anaphylactic-like

reactions to sugammadex are becoming increasingly recognized. Not all reactions have been shown definitively to be true IgE antibody-mediated immediate allergic responses, and there is a lack of consistency in the terminology used by investigators in their diagnostic conclusions. Reactions, at least some IgE mediated, also occur in response to the sugammadex-rocuronium complex. Progress has been made in identifying the fine-structural recognition of the complex. The relative incidences of reactions to free and complexed sugammadex and a comparison of the fine structural allergenic determinants recognized on each, remain to be determined and compared.

Introduction

Sugammadex, a chemically modified γ-cyclodextrin composed of eight *D*-glucopyranoside units in rigid $^4C_1$ conformation linked α(1-4) around a central cavity [1•, 2•], was designed to reverse neuromuscular blockade by encapsulating steroidal neuromuscular blocking drugs (NMBDs), particularly the widely used rocuronium (Fig. 1), but not non-steroidal NMBDs [3–5]. Sugammadex has also been applied to reverse vecuronium-induced block [6] but there have been few clinical studies with

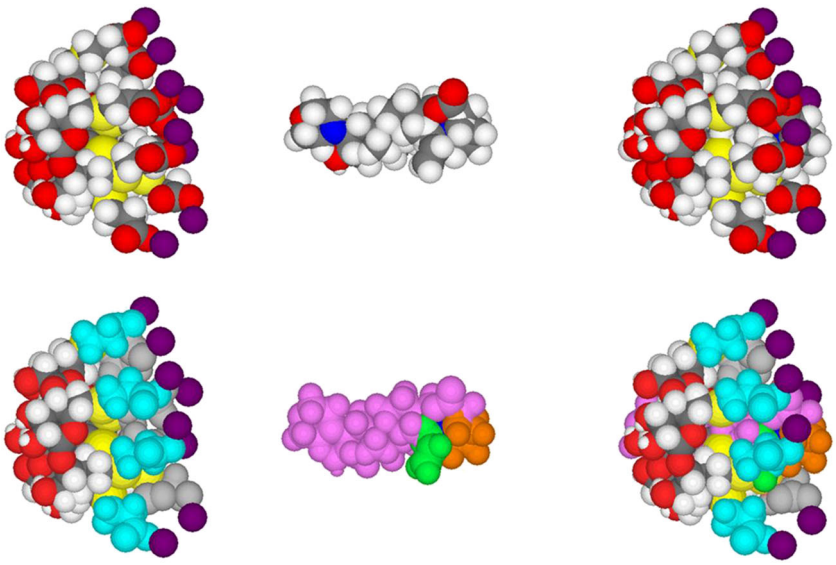

Fig. 1. Corey-Pauling-Koltun (CPK) molecular models of sugammadex, rocuronium, and the host-guest complex of rocuronium with sugammadex. Top line, conventional colors for atoms. Rocuronium (middle structure) reacts with sugammadex (left structure) forming the sugammadex-rocuronium inclusion complex (right structure). Bottom line, coloring changed to distinguish the rocuronium structure from sugammadex. Pyrrolidinium group of rocuronium colored brown; allyl group green; rest of rocuronium molecule light purple. Conventional colors for sugammadex except for the eight thio(2-carboxyethyl) sodium groups each linked to a glucopyranose unit of γ-cyclodextrin to form the selective relaxant binding agent. The 2-carboxyethyl groups of the four thio(2-carboxyethyl) sodium groups visible in the front view are shown in light blue, the sulfur atoms in yellow, and sodium atoms violet; for the four thio(2-carboxyethyl) sodium groups on the other side of the sugammadex molecule, the 2-carboxyethyl groups are shown in gray with, again, the sulfur atoms in yellow and sodium atoms violet. Conventional colors shown are H white, C black, O red, N blue, S yellow, and Na violet

the less often used steroidal NMBDs pancuronium and pipecuronium [7, 8].

Sugammadex was approved by the European Medicines Agency (EMA) in 2008 and the US Food and Drug Administration (FDA) in 2015 after two previous rejections and in the face of criticisms that the apparent incidence of anaphylaxis to the selective binding agent was said to be higher than most other drugs (1 in 299 compared with 1 in 3500–25,000) [9]. By 2016, sugammadex had received regulatory approval in more than 70 countries. It has now become apparent that adverse reactions to the drug, variously diagnosed as allergy, hypersensitivity, hypotension, bronchospasm, anaphylaxis, and anaphylactoid responses, can occur, may be severe, rapid in action, and judging by results from Japan, will increase significantly with increased usage of the drug.

Allergy, hypersensitivity, anaphylaxis, and revised nomenclature

Each of the terms "allergy," "hypersensitivity," and "anaphylaxis" have not always been used consistently and uniformly to mean the same thing, especially by practitioners in different disciplines. To allergists and clinical immunologists "immediate hypersensitivity" is synonymous with a type I, IgE antibody-mediated allergic reaction, "delayed hypersensitivity" means a type-IV cell-mediated reaction while antibody-dependent cytotoxic type-II and immune complex-mediated type-III hypersensitivities make up the four categories in the Gell and Coombs classification of hypersensitivity reactions [10]. The relatively recently suggested revised nomenclature promoted by the European Academy of Allergology and Clinical Immunology and the World Allergy Organization [11] recommending use of the terms "allergic and non-allergic hypersensitivity," "allergic anaphylaxis," "IgE-mediated allergic anaphylaxis," "and nonallergic anaphylaxis" has not helped a situation where confusion and misuse of terms is not uncommon. The suggested new nomenclature to define anaphylaxis is, for many, cumbersome and contentious. At present, the term "anaphylaxis" is used to define an immediate type-I immune reaction mediated by IgE (and sometimes IgG) antibodies whereas the term "anaphylactoid" is reserved for reactions that show similar or even identical symptoms to anaphylaxis but where evidence of an immune basis for the reaction has not been established. As with the term hypersensitivity which is currently applied to a heterogeneous group of mild to severe reactions, until more mechanistic insights are obtained for many so-called sensitivities, intolerances, and pseudoallergic reactions [12–16], it is difficult to see what advantage there is in substituting "IgE-dependent (mediated) allergic anaphylaxis" for "anaphylaxis" and "(IgE-independent) non-allergic anaphylaxis" for "anaphylactoid". Certainly, in itself, the change in nomenclature does little to aid efforts to better understand and define these severe reactions. If long-standing and useful terminology is to be improved, it should be done when mechanistic and clinical insights are far more advanced, comprehensive, and precise than they now are.

Early observations of adverse reactions to sugammadex

In a randomized, double-blind, placebo-controlled study of the effects of sugammadex on QTc prolongation, doses up to 32 mg/kg were administered to 80 healthy male and female patients. One subject discontinued the study after

administration of sugammadex because of a possible hypersensitivity reaction, experiencing dysgeusia, a burning sensation, nausea, abdominal cramps, and a skin rash after sugammadex infusion. Skin prick tests (SPTs) and intradermal tests IDTs) on the subject proved negative to sugammadex, no antibodies to the drug were detected, and tryptase levels were not elevated [17]. A randomized double-blind, crossover, placebo-controlled study of 13 healthy adults 18–65 years old examining safety and tolerability of high doses of sugammadex up to 96 mg/kg revealed one subject who experienced a number of adverse events including skin flushing and an abdominal erythematous rash after infusion of sugammadex 8.4 mg/kg of a 32-mg/kg dose. Serum tryptase relative to normal levels were elevated and intracutaneous testing with sugammadex solution 0.1 mg/ml produced a positive result, indicating a probable hypersensitivity to the agent [18].

Anaphylaxis to sugammadex in Japan

There are reports of more than 40 cases of anaphylactic, anaphylactoid, hypersensitivity, or "allergic" reactions to sugammadex in the medical literature and many more in Japan where the agent has been used since 2010, and sales are number 1 worldwide with 11,054,680 vials sold for the 7-year period April 2010–June 2017. For this period, the Japanese Phamaceuticals and Medical Devices Agency (PMDA) database for adverse events recorded 284 cases of sugammadex-induced reactions. Based on PMDA figures, the incidence of sugammadex-induced anaphylaxis has been estimated to be 1 in 40,000 (0.0025%). Perhaps reflecting its high usage, the Japanese Society of Anesthesiologists (JSA) has issued five warnings since 2011 concerning sugammadex's involvement in, and potential for, provoking anaphylactic shock. A 2013 warning covering the period April 2010–January 2013 reported 95 hypersensitivity reactions, 78 of which were determined to be anaphylactic. The Society has reported an incidence of sugammadex-associated anaphlaxis of 1 in 34,483 (0.0029%) [19]. In a recent Japanese study involving 15,479 patients who received sugammadex, the incidence of anaphylaxis potentially caused by its use was found to be 0.039% (6 patients), an incidence similar to that for succinylcholine and rocuronium [20, 21•]. A study over a 4-year period 2012–2016 to determine the drugs most often provoking anaphylaxis in Japan revealed sugammadex as number 1 (32% of cases), followed by rocuronium (27%) and antibiotics (23%) [22•].

Case reports of possible hypersensitivity reactions to sugammadex

Table 1 summarizes important details of published case reports on 33 severe reactions following the administration of sugammadex [23–47]. Information presented covers patient details; drugs given prior to sugammadex; measures undertaken to treat the reactions; the dose of sugammadex administered; patient responses to the administered sugammadex; the temporal relationship between the administration of sugammadex and the observed response; the drugs administered and other measures undertaken to treat the reactions;

Table 1. Summary of reports of sugammadex-induced reactions and diagnostic conclusions

Patient No. (sex and age) [ref]	Drugs administered prior to sugammadex	Sugammadex dose	Signs and symptoms and time of their first appearance after sugammadex	Treatment	Outcome	Diagnostic tests	Authors' diagnosis
1 (M/17)[a] [23]	Midazolam; bupivacaine; fentanyl; propofol; rocuronium; sevoflurane; cefazolin; acetaminophen; dexketoprofen; ondansetron	200 mg (3.2 mg/kg)	1 min later erythema over thorax; lip and palpebral edema; BP from 120–140/80–90 → 78/32 mmHg; HR from 70–85 → 100–110 bpm; SaO_2 from 99 → 93–94%; bilateral wheeze (0.925 mg/kg)	Hydrocortisone; methyl prednisolone; dextrochlor pheniramine; salbutamol puffs	Trachea extubated 2.75 h later; no wheeze or erythema, little edema	SPT + to sugammadex only[b]; histamine ↑ 30 min; tryptase normal range	Allergy to sugammadex
2 (F/33) [24]	Acetaminophen; midazolam; propofol; fentanyl; rocuronium; dexamethasone; sevoflurane	50 mg		10 min later severe hypotension; lowest BP 50/30 mmHg	Etilefrine; phenylephrine; normal saline; gelatin	BP normal within 15 min. Full recovery	None
Hypotension induced by sugammadex readily treated with sympathomimetics							
3 (M/17) [25]	Propofol; pentazocine; rocuronium; sevoflurane; N_2O	Dose not provided	2 min later redness and wheal on trunk; SpO_2 ↓	Epinephrine repeated doses and infusion	Cutaneous reactions improved and SpO_2 stabilized; moved to ICU and recovery uneventful	None	Anaphylaxis to sugammadex
4 (M/62) [26]	Propofol; remifentanil; rocuronium; amoxicillin/clavulanic acid	150 mg (2.3 mg/kg)	Within 3 min erythema; BP ↓ < 45 mmHg; tachycardia 150 bpm; SaO_2 ↓ < 40%; no bronchospasm	Epinephrine bolus; ventilated	Weaned from epinephrine and mechanical ventilation in ICU	SPT and IDT + to sugammadex only[c]; histamine ↑ (> 100 nmol/l[d]); tryptase normal	Allergic or "non-allergic" hypersensitivity
5 (F/41) [27]	Propofol; remifentanil; rocuronium; sevoflurane cefoperazone/ sulbactam	100 mg (1.9 mg/kg)	3 min later facial edema, blepharedema; no hypotension, tachycardia, or bronchospasm	Hydroxyzine pamoate IV	Cutaneous symptoms improved 9 min after sugammadex	SPT + to sugammadex solution[e] (1–10). No other drugs tested	Suspected hypersensitivity to sugammadex
6 (F/52) [27]	Propofol; remifentanil; rocuronium; ephedrine; atropine; fentanyl; flurbiprofen axetil; mepivacaine; ropivacaine	100 mg (1.9 mg/kg)	3 min later hypotension, syst BP < 50 mmHg, tachycardia 110 bpm; SaO_2 from 99 → 83%; general erythema; peak airway pressure from 24 → 33 mmHg within 5 min of sugammadex administration	Continuous IV infusion epinephrine; norepinephrine; methylprednisolone	Improved 42 min after start of resuscitation; extubated 23 h later	SPT + (5 mm) to sugammadex solution (1–1000). No other drugs tested	Suspected hypersensitivity to sugammadex
7 (F/89) [27]						None	

Table 1. (Continued)

Patient No. (sex and age) [ref]	Drugs administered prior to sugammadex	Sugammadex dose	Signs and symptoms and time of their first appearance after sugammadex	Treatment	Outcome	Diagnostic tests	Authors' diagnosis
	Propofol; remifentanil; rocuronium; ephedrine; atropine; fentanyl sevoflurane; phenylephrine	100 mg (2.2 mg/kg)	7 min after sugammadex wheeze on auscultation; SaO_2 from 99 → 91%; HR 110 bpm; erythema on arm	Methylprednisolone; aminophylline; 2 puffs procaterol/ O_2	Improved within 30 min		Suspected hypersensitivity to sugammadex
8 (M/7)[f] [28]	Propofol; remifentanil; rocuronium; atropine SO_4; lidocaine	40 mg (3.3 mg/kg)	3 min later upper airways distress and paradoxical respiration; SaO_2 82%; prior to treatment BP 120–80/90–40 mmHg and HR 80–120 bpm	Ventilation with O_2 until SaO_2 100%; epinephrine; hydrocortisone	10 min later BP 126/84 mmHg; upper airway stenosis and wheals disappeared ~8 min after epinephrine/ hydrocortisone	"Parents refused allergy tests"	Hypersensitivity probably induced by sugammadex[g]
9 (M/37)[h] [29]	Propofol; remifentanil; rocuronium; lidocaine; cefazolin; droperidol; ropivacaine; (latex catheter) [i]	120 mg (2.1 mg/kg)	Baseline BP 90/40–110/60 mmHg, HR 60–70 bpm; 1 min later BP 86/48 mmHg, HR ↑ to 100 bpm; BP 47/29 mmHg 8 min after sugammadex; wheals on body, swollen lips, palpebral	Ephedrine; HES; hydroxyzine; methylprednisolone;	BP restored to 128/48 mm after phenylephrine and fluids over10min; wheals faded	LST	Anaphylaxis to sugammadex
10 (M/13) [30]	Propofol; remifentanil; rocuronium; sevoflurane; flurbiprofen axetil	80 mg (2 mg/kg)	Baseline PB 116/78, was mostly 90/40 mmHg but syst BP 30 to undetectable after sugammadex; tachycardia 150–160 bpm; cough; global swelling of face; low consciousness	Hydrocortisone; epinephrine; reintubated propofol/ rocuronium; aminophylline; hydrocortisone	Extubated in ICU 17 h after	SPTs + only to sugammadex (1–1000)	Suspected anaphylaxis to sugammadex
11 (F/75) [30]	Propofol; remifentanil; rocuronium; sevoflurane; flurbiprofen axetil	200 mg (2.8 mg/kg)	(a) 10 min after induction and *before* sugammadex, BP and HR ↓ to 70/50 mmHg, 50 bpm; (b) 3 min *after* sugammadex syst BP fell to 40/ undetectable mmHg; erythema precordium; no respiratory symptoms	Ephedrine, phenylephrine, atropine; chlorpheniramine; ranitidine; hydrocortisone	(a) BP and HR returned to 150/70 mm and 75 bpm. (b) BP grad. ↑ to 160/80 mmHg; extubated 15 h later	IDTs + only to sugammadex (1–100)	Suspected anaphylaxis to sugammadex
12 (M/34) [30]	Propofol; remifentanil; rocuronium; sevoflurane;	200 mg (3.2 mg/kg)	1 min later erythema all over body; BP ↓ from 100/60 to	Ephedrine; chlorpheniramine;	BP recovered to 100/60 mmHg; erythema	IDTs + only to sugammadex	Suspected anaphylaxis to sugammadex

Table 1. (Continued)

Patient No. (sex and age) [ref]	Drugs administered prior to sugammadex	Sugammadex dose	Signs and symptoms and time of their first appearance after sugammadex	Treatment	Outcome	Diagnostic tests	Authors' diagnosis
	flurbiprofen axetil; pentazocine		70/40 mmHg; no respiratory symptoms	ranitidine to treat erythema	resolved; discharged after 6 days	1–100 and ± to 1–1000	
13 (F/29) [31]	Propofol; rocuronium, fentanyl; parecoxib; dexamethasone, droperidol; cefazolin	200 mg (2 mg/kg)	hypotensive within 3 min (BP 30–40 mmHg); tachycardic (HR 125 bpm); reduced cardiac output; generalized edema for several days	Metaraminol; epinephrine; sodium lactate; phenylephrine infusion	Extubated 2.5 h after sugammadex; generalized edema persisted for several days	IDTs + only to sugammadex 1–100 and 1–1000 [j]; tryptase at 2, 6, and 18 h 59, 32.2, and 6.3 µg/l, respectively	Anaphylaxis to sugammadex
14 (F/15) [31]	Propofol; rocuronium, fentanyl; midazolam; parecoxib; morphine; dexamethasone, granisetron; cephazolin; acetaminophen; clonidine	100 mg dose/kg not provided	Rash covering face, arms and trunk within minutes; facial swelling; hypotension	Reintubation; epinephrine boluses and infusion; hydrocortisone; promethazine	Information not supplied	IDTs + only to sugammadex 1–100, 1–1000. Tryptase normal	Anaphylaxis to sugammadex
15 (F/33) [31]	propofol; rocuronium, fentanyl; dexamethasone; cefazolin; chlorhexidine; acetaminophen; ondansetron	200 mg plus 200 mg after reaction. Dose/kg not provided	Severe bronchospasm almost immediately after sugammadex; rapid fall in SaO_2 to 58%	Sugammadex (200 mg); inhaled and IV salbutamol	Recovery uneventful	IDTs + only to sugammadex 1–100[j]	Anaphylaxis to sugammadex
16 (M/56) [32]	Propofol; rocuronium, fentanyl; desflurane; O_2; ropivacaine; granisetron; dexamethasone; heparin; droperidol; cefazolin; crystalloid; albumin	200 mg dose/kg not provided	Severe circulatory shock 1 min after sugammadex (BP 40/30 mmHg) with tachycardia (HR 104 bpm)	O_2; fluids (crystalloid, gelatin); IV epinephrine boluses and infusion	Slow reduction of epinephrine infusion led to uneventful recovery	IDTs + only to sugammadex 1–100 and 1–1000; tryptase + (93 µg/l)	Anaphylaxis to sugammadex
17 (F/12) [33]	Propofol; remifentanil; rocuronium; sevoflurane	160 mg (4 mg/kg)	2 failed intubations; 3 min after sugammadex ↓SaO_2 (75%); difficult ventilation; airways distress; BP 60/40 mmHg; severe bradycardia	Epinephrine IV and infusion; hydrocortisone; fluids; diphenhydramine	Transferred to ICU then pediatric ward; improved with no complications	Parents refused allergy tests	Possible allergic reaction to sugammadex
18 (F/67) [34]	Propofol; rocuronium, fentanyl; isoflurane; amiodarone	200 mg dose/kg not provided	2 min after sugammadex PIP rose to 45 cm H_2O; BP 70/40 mmHg; ventricular rate ↑ 140–160 bpm; erythema and urticaria of chest wall; ↓ airflow; expiratory wheeze	Epinephrine; hydrocortisone; albumin	Patient "improved dramatically" as measured by PIP, BP, and less wheezing	None	Anaphylaxis to sugammadex
19 (F/69) [35]	Pentothal sodium; O_2–N_2O mix;	100 mg (2 mg/kg)	3 min after sugammadex patient extubated;	Crystalloid; hydrocortisone;	Improved after 70 min; no	None	Anaphylaxis to sugammadex

Table 1. (Continued)

Patient No. (sex and age) [ref]	Drugs administered prior to sugammadex	Sugammadex dose	Signs and symptoms and time of their first appearance after sugammadex	Treatment	Outcome	Diagnostic tests	Authors' diagnosis
	rocuronium, sevoflurane		5 min later erythema, oropharyngeal itching, palpitations developed; BP 49/30 mmHg; tachycardia 110–120 bpm	ephedrine; bolus and IV infusion of phenylephrine	complications; discharged 48 h after reaction		
20 (M/74) [36]	Propofol; remifentanil; rocuronium; sevoflurane	Dose not provided	2 min later, redness, tachycardia, hypotension, itchiness	Steroids, epinephrine, antihistamine	Improved; 3 h later in ICU, biphasic reaction with dyspnea and BP↓; treated with steroids, epinephrine, beta-agonist; discharged following day	None	Biphasic anaphylactic attack
21 (M/82) [37]	Propofol; remifentanil; rocuronium; desflurane	Dose not provided	3 min after sugammadex hypotension, tachycardia; wheal and redness on trunk and limbs	Epinephrine; corticosteroids; crystalloid	Hemodynamics recovered; wheal and redness gradually faded. Recovery uneventful	None	Anaphylaxis to sugammadex
22 (F/60) [38]	Propofol; remifentanil; rocuronium; ephedrine; phenylephrine; fentanyl; lignocaine; flurbiprofen axetil; idiocyanine green; sulbactam-ampicillin; atropine	200 mg (4 mg/kg)	3 min after sugammadex BP 66/34 mmHg; bilateral palpebral swellings	Epinephrine infusion	Postoperative mild gastric irritation. Discharged 10 days later	SPT + to sugammadex 1–1000, 1–10 and undiluted[k]. No other drugs tested	Anaphylaxis to sugammadex
23 (M/50) [39]	Propofol; acetaminophen; fentanyl; rocuronium; gentamycin; morphine; chlorhexidine; omnipaque	200 mg dose/kg not provided	Within 5 min hypotension (BP 45 mmHg); tachycardia (HR 106/min); desaturation (81%); generalized urticaria	Epinephrine; hydrocortisone; chlorphenamine	Information not supplied	SPT + to sugammadex 1:1. IDT + to sugammadex 1–100 and 1–1000[l]; tryptase + (81 μg/l)	Anaphylaxis to sugammadex
24 (M/62) [39]	Propofol; rocuronium; fentanyl; ondansetron; dexamethasone; co-amoxiclav	400 mg dose/kg not provided	Within 5 min hypotension (BP 60 mmHg); diaphoresis; unresponsiveness	Epinephrine; hydrocortisone; chlorphenamine	Information not supplied	SPT + to sugammadex. IDT + to sugammadex 1–100 and 1–1000[l]; tryptase + (141 μg/l)	Anaphylaxis to sugammadex

Table 1. (Continued)

Patient No. (sex and age) [ref]	Drugs administered prior to sugammadex	Sugammadex dose	Signs and symptoms and time of their first appearance after sugammadex	Treatment	Outcome	Diagnostic tests	Authors' diagnosis
25 (M/63)[a] [39]	Propofol; acetaminophen; remifentanil; rocuronium; ondansetron; gentamycin; ranitidine; ketamine; cyclizine + dexamethasone	100 mg dose/kg not provided	Within 5 min hypotension (BP 66 mmHg); tachycardia (HR 118/min); desaturation (50%); generalized urticaria	Epinephrine; hydrocortisone; chlorphenamine	Information not supplied	IDT + to sugammadex 1–100 and 1–1000[l]; tryptase + (36 μg/l)	Anaphylaxis to sugammadex
26 (F/65) [40]	Propofol; rocuronium; fentanyl; lidocaine; sevoflurane; flubiprofen axetil; acetaminophen; cefotiam	200 mg dose/kg not provided	2 min after sugammadex hypotension (BP < 60 mmHg); erythema over whole body	Ephedrine; hydrocortisone; sodium succinate	Symptoms improved after treatment and patient recovered	IDTs + only to sugammadex 1–1000 and 1–10,000	Anaphylaxis to sugammadex
27[m,n] (F/19) [41]	Propofol; remifentanil; rocuronium; fentanyl; cefazolin; flurbipropen	Dose not provided	5 min after sugammadex SpO_2 and end-tidal CO_2 ↓; bronchospasm; wheezing; erythema over chest and face; BP ↓ from 100 to 50 mmHg; HR 140/bpm	Epinephrine; hydrocortisone; crystalloid	Extubated uneventfully 3 h later	IDT + to undiluted sugammadex[o] and + to rocuronium 1–1000[p]; LST negative; tryptase levels normal	Anaphylaxis to sugammadex
28 (M/35) [42]	Propofol; remifentanil; rocuronium; fentanyl; sevoflurane; lidocaine	200 mg (1.8 mg/kg)	2 min after sugammadex and extubation erythema over whole body; dyspnea; BP 65/38 mmHg; HR 130/min; SpO_2 83%; wheezing	Dexamethasone, salbutamol nebulizer and dexchlor pheniramine then epinephrine; fluids	Improvement 20 min after epinephrine; discharged after 5 days	SPT weakly + only to 1:1 sugammadex[o]	Suspected anaphylaxis to sugammadex
29 (M/62) [43]	Propofol; remifentanil; desflurane; rocuronium	100 mg (0.7 mg/kg)	4 min after sugammadex SAP < 70 mmHg; widespread erythema	Metaraminol; ephedrine; crystalloid; epinephrine boluses and IV infusion; hydrocortisone; chlorpheniramine	In ICU epinephrine infusion continued 7.5 h; extubated 23 h later. Discharged a week later	SPT and IDT + to sugammadex 1–1000; tryptase + shortly after CV collapse, at 6 and 12 h (49.6, 36.6, 15.4 μg/l), respectively	Anaphylaxis to sugammadex
30 (M/73) [44]	Propofol; remifentanil; rocuronium; fentanyl; sevoflurane	200 mg (2.6 mg/kg)	6 min after sugammadex BP not measurable; ST depression; PVC; 14 min after sugammadex unconscious and entire body flushed	Phenylephrine and fluid; epinephrine; lidocaine; nicorandil; methylprednisolone; hydroxyzine HCl	Recovered consciousness 1 h after shock	IDT + to 1:1 sugammadex[o]; tryptase ↑	Anaphylaxis to sugammadex resulting in cardiac arrest
31 (F/22)[q] [45]	Propofol; remifentanil; rocuronium; cefazolin; lidocaine	340 mg (4 mg/kg)	Immediately after sugammadex BP ↓ to 43/25 mmHg and HR ↓ to 43 bpm; arrhythmia;	Ephedrine; epinephrine; lidocaine; pheniramine; methylprednisolone; famotidine;	Extubated 3 h after sugammadex with no bronchospasm and wheezing	No skin tests; tryptase normal serum levels	Suspected anaphylaxis to sugammadex

Table 1. (Continued)

Patient No. (sex and age) [ref]	Drugs administered prior to sugammadex	Sugammadex dose	Signs and symptoms and time of their first appearance after sugammadex	Treatment	Outcome	Diagnostic tests	Authors' diagnosis
			PVC; flushing; SpO_2 86%; airway pressure	norepinephrine infusion			
32 (F/18) [46]	Propofol; remifentanil; rocuronium; sevoflurane; cefazolin; lidocaine with epinephrine; acetaminophen	200 mg (3.5 mg/kg)	3 min after sugammadex abdominal pain, nausea, urge to urinate; BP 78/41 mmHg; HR 140 bpm; SpO_2 71%; cyanosis of fingers; flushing lower limbs	Ephedrine; epinephrine	Recovered POD 1, discharged POD 3	Stated that SPTs were + to sugammadex but no concentrations provided	Anaphylaxis to sugammadex
33 (M/60) [47]	Midazolam; nicardipine; propofol; remifentanil; succinylcholine; desflurane; rocuronium	200 mg (3.1 mg/ml)	3 min after extubation BP ↓ to 78/38 mmHg; after ephedrine and phenylephrine and transfer to PACU, whole body urticaria, BP 66/41 mmHg, tachycardia 105 bpm	Ephedrine; phenylephrine; epinephrine; norepinephrine; methylprednisolone; hydrocortisone; pheniramine	Condition improved after 30 min	IDT + to sugammadex 1–100 and 1–1000 and sugammadex-rocuronium complex[r,s]; tryptase in normal range[t]	Anaphylaxis to sugammadex and sugammadex-rocuronium complex

BP, blood pressure; *bpm*, beats per minute; *CV*, cardiovascular; *HES*, hydroxyethyl starch; *HR*, heart rate; *ICU*, intensive care unit; *IDT*, intradermal test; *IV*, intravenous; *LST*, lymphocyte stimulation test; *PACU*, post-anesthesia care unit; *PIP*, peak inspiratory pressure; *POD*, postoperative day; *PVC*, premature ventricular contraction; SaO_2, percentage of hemoglobin in arterial blood saturated with oxygen; *SAP*, systolic arterial pressure; SpO_2, peripheral capillary oxygen saturation; *SPT*, skin prick test; "↑" elevation; "↓" decrease; "→" changed to

[a]No previous exposure to sugammadex

[b]All drugs used during anesthesia were skin tested; no concentration of sugammadex test solution given

[c]SPT, 100 mg/ml; intradermal test (IDT), 0.1 mg/ml

[d]Normal value < 10 nmol/l

[e]Sugammadex solution 100 mg/ml

[f]Uneventful surgery 1 month earlier when given propofol, remifentanil, rocuronium, sevoflurane, N_2O, levobupivacaine, atropine SO_4, and neostigmine

[g]Authors also refer to reaction as "anaphylaxis"

[h]History of allergy to shrimp and crab

[i]No history of latex allergy

[j]An IDT rocuronium-sugammadex mix produced an attenuated skin response compared with the 1–1000 dilution of sugammadex

[k]A positive SPT was also obtained with an undiluted solution of rocuronium-sugammadex mixture

[l]No other drugs tested

[m]Patient had a medical history of asthma

[n]Patient diagnosed with anaphylaxis in two different surgeries: data shown are details of a reaction to sugammadex during the first surgery. During general anesthesia 22 days later, the patient was diagnosed with anaphylaxis to rocuronium

[o]A concentration (50 mg/ml) likely to be irritant intradermally

[p]Undiluted solutions of sugammadex and rocuronium are 100 and 10 mg/ml, respectively

[q]Patient with Weaver syndrome

[r]To prepare the complex, sugammadex (1–500) was mixed with the same volume of rocuronium (1–50). Thus, the final dilutions of the two drugs were 1–1000 and 1–100, respectively

[s]Skin test result to rocuronium was negative

[t]Authors state: "the proper sampling time for detection of plasma histamine and serum tryptase had passed"

outcomes for the patients; diagnostic investigations undertaken if any; and authors' diagnostic conclusions. As mentioned, reactions to the drug in Japan have been far more numerous than elsewhere perhaps at least partly because of heavier usage and the countries' health insurance system that provides substantial financial relief for patients [22•]. The high number of cases is reflected in the Japanese literature, but only a small number have been considered in this review due to the difficulty of extracting all the relevant information from the reports published in Japanese (see, for example, [48, 49]).

Box 1 summarizes the most important and interesting findings from Table 1 and a more detailed analysis follows.

Box 1. Summary of clinical details, observed reactions, and diagnostic conclusions from the 33 individual case reports detailed in Table 1

- 33 patients; age range 7-89 years; 17 male, 16 female
- Dosage range of sugammadex administered 0.7-4 mg/kg[a]
- Times of first appearance of signs and symptoms after administration of sugammadex: ≤ 3 minutes, 23 patients; > 3 ≤ 5 minutes, 4 patients; > 5 ≤ 10 minutes, 4 patients; no time stated for patient 10, response "within minutes" for patient 14
- Skin tests with sugammadex undertaken on 22 patients, 19 positive; possible irritant concentrations used for 2 patients (numbers 27, 30); concentrations not stated for 1 patient (number 32); 11 not tested
- Serum tryptase concentrations determined for 13 patients; positive for 6 patients (numbers 13, 16, 23, 24, 25, 29); said to be elevated in patient 30 but no figures provided
- Most common reaction symptoms: hypotension; tachycardia; decreased oxygen saturation; facial edema; itching; erythema, often widespread; bronchospasm; flushing
- Pharmacological therapy: sympathomimetic drugs – epinephrine, ephedrine, phenylephrine, metaraminol; steroids – hydrocortisone, methylprednisolone, dexamethasone; H_1 and H_2 antihistamines; salbutamol and aminophylline for bronchodilation/airway obstruction
- Six patients showed symptoms of wheeze and/or bronchospasm
- Patient 15's symptoms resolved after salbutamol and no epinephrine: anaphylaxis or severe asthma? (See text)
- Authors' diagnoses of reactions to sugammadex: Allergy (1 patient); possible allergic reaction (1); hypotension (1); allergic or non-allergic hypersensitivity (1); suspected hypersensitivity (3); suspected anaphylaxis (6); anaphylaxis (18); biphasic anaphylaxis (1); anaphylactic reaction to sugammadex-rocuronium complex as well as sugammadex (1)

[a]Dosage not provided for patients 3, 20, 21, 27. Insufficient information supplied to calculate dose/kg for patients 14, 15, 16, 18, 23, 24, 25, 26

Sugammadex dose

Reactions to the reversing agent occurred following the administration of doses ranging from 0.7 to 4 mg/kg. The dose of sugammadex administered was not provided for four patients while for a further eight, the absence of the patient's weight precluded information on the dose-per-kilogram basis (Table 1; Box 1). In two randomized, double-blind, placebo-controlled studies of the potential and incidence of hypersensitivity after sugammadex administration to healthy volunteers, hypersensitivity was confirmed in 10 of 151 subjects (6.6%) given sugammadex 4 mg/kg, 14 of 148 (9.5%) given 16 mg/kg, and 1 of 76 (1.3%) given placebo. One subject given sugammadex 16 mg/kg experienced

anaphylaxis [50]. In the second trial, hypersensitivity was diagnosed in 1 of 148 subjects (0.7%) given sugammadex 4 mg/kg, 7 of 150 (4.7%) given 16 mg/kg, and 0 of 150 given placebo. Again, there was one case of anaphylaxis in the 16-mg/kg group [51]. Of 597 subjects given sugammadex in the two trials, what was judged to be hypersensitivity resulted in 32 subjects and anaphylaxis in 2 subjects, incidences of 5.4 and 0.33%, respectively. These figures are considerably higher than seen so far in clinical practice.

Time of appearance of symptoms

The time of first appearance of signs and symptoms after administration of sugammadex was 5 min or less in 27 of the 33 patients (82%); 23 patients (70%) showed symptoms within 3 min, but there are a few cases when symptoms manifested more slowly, for example, after 6, 7, 8, and 10 min in the 33 patients (12.1%) considered here (Table 1; Box 1) and after a delayed onset of 15 min in the recovery room after anesthesia [52]. Of cases reported to the JSA (see above), the onset of sugammadex-induced reactions occurred within 5 and 10 min of administration for 65.8 and 86.8% of cases, respectively. Because sugammadex is often administered not long before removal of the patient to the postoperative recovery area and occasional delayed reactions (~ 15 min) have been noted, patients given the reversing agent should be observed carefully in the operating room for at least 5 min after administration and closely monitored during transport [22•].

Skin tests

In reviewing the original case reports and information in Table 1 and Box 1, two points concerning the skin test findings should be kept in mind. Firstly, many, if not most, of the reports refer to sugammadex solution for skin testing without also mentioning the initial concentrations of the sugammadex solutions used to prepare the dilutions for skin testing. In these cases, it is highly likely that the commercial formulation containing 100 mg/ml sugammadex was used to prepare dilutions and sometimes as a neat solution. Likewise, when rocuronium solutions were used for skin testing, the commercial product containing 10 mg of drug/ml was probably the source preparation. Recommended skin test concentrations [53] for sugammadex are 100 mg/ml for skin prick testing, and for IDT, 100 μg/ml as an initial test up to a maximum of 1000 μg/ml, in other words a 1:1000 and 1:100 dilution of the commercial solution, respectively. Irritant concentrations of sugammadex were used in IDTs on at least two patients. Secondly, in Table 1, when skin test results are stated as positive *only* to sugammadex, it should be understood that in most cases other administered drugs were also tested but proved negative.

Tryptase tests

Serial serum tryptase measurements are a valuable addition to the clinical assessments and diagnostic measures undertaken in the diagnosis of perioperative anaphylaxis [54–56], but despite this, there seems to be a need to raise awareness of the test among anesthetists [57]. The test was applied to only 13 of

the 33 patients (39%) reviewed here (Table 1; Box 1). While little or no changes in tryptase serum concentrations do not necessarily preclude a diagnosis of anaphylaxis, rising levels in the period 15 min to 3 h after onset of symptoms followed by decline is highly predictive. The enzyme has a half-life of about 2 h so the time of sampling is important but, as is the case in the present series of case reports, information on sampling times is often not provided. Two methods of interpretation of the test have been used—the absolute acute-phase measurement of tryptase and the percentage change from baseline. Both methods have been found to be comparable [58].

Clinical presentation and bronchospasm

Table 1 and Box 1 list the most commonly occurring adverse symptoms provoked by sugammadex in the 33 cases examined. Hypotension, often the earliest sign, desaturation, and erythema were seen in many of the patients. Bronchospasm, described as the clinical feature of exacerbated underlying airway activity with the potential to become an anesthetic disaster [59, 60] appears to have an interesting link with sugammadex. In 2018, 44 cases of bronchospasm and 6 of arteriospasm formed part of 698 adverse event case reports on sugammadex in the US FDA Adverse Event Reporting System (FAERS) database. In a 2018 Internet posting concerning potential signals of a serious risk and new safety information, the FDA announced that it was evaluating the need for regulatory action in relation to the possible association of sugammadex injection (Bridion) with bronchospasm and laryngospasm [61•]. These potential signals of risk and safety were identified from the FAERS database. Soon after, the FAERS database was utilized to undertake retrospective pharmacovigilance signal analyses, in this case so-called disproportionality analyses, to determine if the signals between sugammadex and adverse events bronchospasm and coronary arteriospasm are significant[62•]. The analysis essentially compares the expected number of drug-related events with the actual reported number; a high number of the latter indicates disproportionality and a potential statistical association between the drug and the adverse event [63, 64]. The analyses showed that both bronchospasm and arteriospasm were statistically significantly associated with sugammadex for males and females. An association of bronchospasm and sugammadex with age 0–80 years was also apparent.

A search of PubMed containing the words sugammadex and bronchospasm or laryngospasm published between January 2010 and August 2018 found 19 cases of sugammadex-induced bronchospasm or laryngospasm [62•]. Apart from two patients with a history of asthma, the other patients either had not been diagnosed with a pulmonary disease or respiratory issues were not mentioned. In 2012, a phase III, randomized, multicenter, safety-assessor-blinded study was undertaken to evaluate the safety and efficacy of sugammadex for reversal of neuromuscular blockade in 77 patients with pulmonary disease. Two patients with asthma who received desflurane for maintenance of anesthesia and sugammadex 4 mg/ml developed bronchospasm leading the authors to conclude that bronchospasm is a possibility when administered to patients

with underlying pulmonary disease and anticipation of possible bronchospasm is recommended for such patients who might receive sugammadex [65]. Furthermore, three patients without pulmonary disease given desflurane in general anesthesia developed bronchospasm after receiving sugammadex and rocuronium [66] and another case involving sugammadex and desflurane was recently reported [67]. Interestingly, in normal rats, sugammadex did not affect contractile function of bronchial smooth muscle [68].

Only two patients, numbers 15 and 27, showed symptoms of bronchospasm, patients 1, 7, 18, 27, and 28 experienced wheezing, and patients 1, 15, and 28 were given the β_2-adrenergic agonist and bronchodilator salbutamol (Table 1). Patient 27 had a history of asthma, patient 15 did not, and neither patient received desflurane. Treatment of patient 27 (who was also diagnosed with anaphylaxis to rocuronium during a second surgery) was conventional in that treatment consisted of epinephrine with crystalloid and a steroid. For patient 15, no epinephrine or other sympathomimetic agents were administered and treatment consisted of an extra dose of sugammadex plus salbutamol given by inhalation and intravenously [31]. The rationale for the second dose of sugammadex is not clear and despite the positive IDT with sugammadex 1:100, the diagnostic conclusion of anaphylaxis does not appear clear cut. In fact, there is limited information on the frequency of bronchospasm in perioperative anaphylaxis, estimated to occur in 1.7–16% of patients during anesthesia [69, 70]. This seems a surprisingly broad range. Assuming a conservative incidence of 2%, Harper and Cook [52] estimate that bronchospasm presenting as an isolated or first clinical feature during anesthesia is at least 200 times more likely to be due to a mechanism other than anaphylaxis.

Treatment

The direct sympathomimetic epinephrine, the primary treatment and mainstay of management of anaphylaxis, was used in the treatment of 22 of the 33 cases (66.7%). Other sympathomimetics, ephedrine, an indirect stimulant of the adrenergic system, bronchodilator, and treatment for hypotension was employed in nine patients (27.2%), phenylephrine, a selective α_1-adrenergic receptor activator used as a vasopressor for the management of acute hypotension, was used in six patients (18.2%), while the amine metaraminol, used for acute hypotension in anesthesia, was given to only two patients (Table 1). Norepinephrine, administered to three patients, is a potent α-adrenergic receptor agonist and effective for maintaining blood pressure, but unlike phenylephrine, it is also a weak β-adrenergic receptor agonist and thus less likely to decrease heart rate and cardiac output. Surprisingly, steroids, chiefly hydrocortisone and methylprednisolone, were administered to 23 of the 33 patients (69.7%). It has been suggested that their use in anaphylaxis, presumably to help control any late-stage response, may stem from their effectiveness in the long-term management of asthma [52]. A combination of H_1 and H_2 histamine receptor antagonists may improve urticaria and pruritus, but there is a lack of consensus on the possible benefit of antihistamines in the management of anaphylaxis. Despite this, antihistamines were administered to 16 patients

(48.5%). H_1 antihistamines employed were chlorpheniramine, dextrochlorpheniramine, diphenhydramine, hydroxyzine, pheniramine, and promethazine; H_2 antagonists administered were famotidine and ranitidine. Three patients were given both an H_1 and an H_2 antagonist.

Diagnosis

An interesting, if not curious, feature of the authors' diagnoses of the 33 cases detailed in Table 1 and summarized in Box 1, is the lack of uniformity of nomenclature with nine different diagnostic descriptions including simply allergy, "possibly allergic," "suspected hypersensitivity," "suspected anaphylaxis," and "anaphylaxis." This diversity of how reactions should be precisely defined is also reflected in the diagnostic descriptions of the 284 sugammadex-induced reactions listed in the Japanese PMDA database: 157 of the cases were reported as anaphylactic shock, 88 as an anaphylactic reaction, 35 cases reported as an anaphylactoid reaction, and 4 cases as anaphylactoid shock [22•]. Many of the case studies were undertaken in Japan and Korea and while to a certain extent the variety of diagnostic descriptions may reflect the terminology used in the different countries and, as stated by Takazawa et al.[22•], the "variations in the definition of anaphylaxis in Japan," much of the diversity is due to the not infrequent misuse of the terms allergy, hypersensitivity and anaphylaxis and current confusion with, and reluctance by some, to adopt the new terminology currently being promoted (see section above, "Allergy, hypersensitivity, anaphylaxis, and revised nomenclature").

Although there is little information on the histamine- and other mediator-releasing effects of sugammadex, the European Medicines Agency lists urticaria, erythematous rash, flushing, hypotension, tachycardia, and bronchospasm as adverse effects of the agent. Even in the absence of evidence for an immune-mediated reaction, some would identify such signs and symptoms as anaphylaxis. This point appears to be relevant to many of the cases examined here where only 20 of the 33 different reactions were determined to be anaphylaxis to sugammadex even though the number of patients with the relevant symptoms, successfully applied treatments, and supporting skin and tryptase test results were considerably less than 20.

As previously stated [71•], in addition to a carefully observed, gathered, and recorded history of a perioperative reaction to sugammadex together with an expert clinical assessment of temporal aspects of the reaction, signs, symptoms, and responses to treatments, the "ideal combination" of investigative procedures is: "(1) The tryptase test (preferably mature tryptase) performed on the patient's preoperative serum sample and at least one or two samples after the onset of symptoms (e.g., at 30 min up to four (or even) 6 h). (2) Employment of validated sugammadex skin tests—percutaneous, intradermal, or both (together with controls). (3) Application of a specific immunoassay for the detection of sugammadex-reactive IgE antibodies. Such an assay should be used to demonstrate specific serum antibodies in both direct binding and dose-dependent inhibition examinations (together with appropriate controls)." (4) In some cases, basophil activation tests may be useful. Note also that even with

a positive skin test to a non-irritating drug, the test accuracy, i.e., the sensitivity and specificity of the test, remains unknown. This can be achieved by obtaining positive and negative skin test results together with provocation testing which itself involves risk, is time consuming, and often not standardized [12, 72]. With these required investigations in mind, the diagnostic conclusion for many of 33 cases detailed here would be a "suspected anaphylactic" or a "suspected anaphylactoid" reaction to sugammadex. Perhaps the only patients included under the former classification would be numbers 13, 16, 23, 24, 25, 29, and maybe 30 while a number of others with more test results lacking would be classified as suspected anaphylactoid reactions (Table 1). Application of the above tests might be expected to alter such initial tentative classifications for at least some patients.

Reactions to sugammadex complexed with rocuronium

In an early assessment of some allergic implications of the use of cyclodextrin hosts such as sugammadex, Baldo and colleagues in 2011 [2•] drew attention to the potential allergenicity of the host itself and the sugammadex-rocuronium host-guest inclusion complex (S-R-Cx) which could be viewed as a potential compound antigen. It was pointed out that "the possibility of rocuronium-sugammadex inclusion complex provoking an allergic response in a patient not allergic to rocuronium should be kept in mind." With regard to the possibility of causing an allergic response in a patient not allergic to the individual components of the complex, the authors stated: "It would be interesting, and perhaps wise, to use rocuronium, sugammadex, and rocuronium-sugammadex complex in a skin test study to check for induced allergic sensitivity in patients given sugammadex ..." [2•].

At the time of writing, there were seven published reports of anaphylaxis apparently due to S-R-Cx [38, 47, 73–76, 77•]. As with skin testing for suspected allergy to sugammadex, however, it is not always clear in the cases what the starting concentrations of the sugammadex and rocuronium solutions were. As well, when testing was undertaken to look for skin test reactivity to the S-R-Cx, a correct ratio of sugammadex/rocuronium to form the complex was not always used. Sugammadex and rocuroniumn bind in a 1:1 M ratio; the molecular masses of sugammadex and rocuronium are 2178 and 609.7 g/mol, respectively, so 3.57 g of sugammadex binds 1 g of rocuronium bromide. Some skin tests have been carried out with quantities that do not reflect the correct stoichiometric ratio of the inclusion complex due, for example, to the mixing of equal *volumes* of the proprietary drug solutions. As pointed out, a molar excess of either drug in the test solution could make interpretation of the skin test results difficult and thus affect diagnostic conclusions [78]. In most of the studies so far, the 1:1 sugammadex/rocuronium molar ratio for the preparation of S-R-Cx has not been adhered to. As to the timing of skin testing, the undertaking of testing only 4 days after the reaction (compared with 1 month for S-R-Cx) by Kim et al. [76] has been criticized [79].

Consistent with the prediction of "the possible allergenic properties of the cyclodextrin carrier itself and of the drug-carrier compound antigen" [2•], so far small, but increasing numbers, of patients skin test positive to both sugammadex and S-R-Cx [38, 47] and skin test positive to S-R-Cx but negative to sugammadex [73–76, 77•] have been diagnosed with anaphylaxis induced by S-R-Cx. Some progress in elucidating the molecular basis of allergic recognition of the complex was recently made in skin and basophil activation tests and serum IgE immunochemical direct binding and inhibition recognition studies on a patient who was skin test negative to sugammadex, rocuronium, and its steroidal NMBD analogs [77•]. The patient experienced IgE/FcεRI-dependent anaphylaxis to a stoichiometrically prepared sample of S-R-Cx. The IgE antibodies recognized the host-guest complex regardless of the complexed steroidal NMBD and regardless of charge on the complexed guest molecule as shown by recognition of the rocuronium analog desallyl rocuronium. The basis of the immune recognition appears to be a shape alteration involving the thiocarboxyethyl sodium side chains attached at the primary ring of the host sugammadex molecule creating a new allergenic determinant. So far, the numbers of relevant patients are small, but as they accumulate, it will be interesting to compare the incidences of reactions to free and complexed sugammadex and to identify the fine structure of the allergenic determinants recognized on each.

Conclusions

Following numerous reports of severe anaphylactic/allergic-like reactions to sugammadex from Japan where the selective relaxant reversing agent has been used longer and more extensively than elsewhere (and where it is now the leading cause of perioperative anaphylaxis [22•]), it is becoming increasingly apparent that, in the perioperative setting, anesthetists must be mindful of a relatively rare but potentially life-threatening reaction to the drug. Being approved in the USA only since 2015 and now registered in more than 70 countries, the number of case reports of reactions to the drug can be expected to increase substantially, in itself focusing heightened awareness on the drug's safety profile. As summed up by Savic et al. [80]: "There is undisputed evidence of an allergy risk with sugammadex, but it is too early to quantify that risk precisely."

Beyond the clinical interest in sugammadex's novel action, effectiveness in reversing neuromuscular block, safety concerns, and as a possible treatment of rocuronium anaphylaxis [5, 12, 22•], immunological aspects of this chemically modified cyclodextrin and the accompanying implications of its immune recognition may be relevant to the broader subject of drug-carrier inclusion complexes [2•]. Identification of the fine structure of allergenic determinants on sugammadex and its complex with rocuronium, already begun [77•], and extension to immune recognition of unmodified γ-cyclodextrin, other cyclodextrins, S-R-Cxs from different patients, and a comparison of native and denatured sugammadex [81], may have bearing on our clearer understanding of the drug's allergenicity, its potential sensitive patients, safety, and continued usage.

Compliance with Ethics Guidelines

Conflict of Interest
The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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