Review Article

Sugammadex-induced anaphylactic reaction: A systematic review

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Abstract

Perioperative anaphylaxis is a rare, but life-threatening hypersensitivity reaction for patients undergoing surgical procedures. Sugammadex is a relatively new drug used to reverse the neuromuscular blockade of specific anesthetics in surgery. Several case reports indicate that there may be a risk of anaphylaxis associated with the use of sugammadex This review examines the literature in order to evaluate the strength of the association between sugammadex use and anaphylaxis. A query of PubMed, EMBASE, and Web of Science was conducted using a combination of terms to identify relevant articles from inception until March 9, 2020. We included any primary study that identified sugammadex as a probable causative agent based on the World Allergy Organization diagnostic criteria for anaphylaxis. A total of 24 articles were reviewed. Across the three randomized controlled trials, there were only four cases of anaphylaxis identified. Incidence of anaphylaxis was reported in only one trial at 0.33%. Two retrospective observational studies conducted in Japan identified cases of anaphylaxis, with incidences of 0.02 and 0.04%. Among 19 case reports and series, 25 patient cases of anaphylaxis were confirmed via allergy testing to be caused by sugammadex or sugammadex–rocuronium complex. Commonly reported symptoms included hypotension, erythema, and decreased oxygen saturation. Based on the findings of this review, there appears to be a rare, but serious, association of sugammadex-induced perioperative anaphylaxis with an incidence between 0.02 and 0.04% in observational studies. It is unclear whether sugammadex on its own or in complex with rocuronium triggers this reaction, but it is clearly involved in inducing anaphylaxis. Further population studies are needed to get a more accurate global incidence rate, and more detailed allergy testing is required to better describe which step of the sugammadex reversal pathway initiates the anaphylactic attack.

Keywords: Anaphylaxis, hypersensitivity, sugammadex

Introduction

Perioperative anaphylaxis is a rare, but life-threatening hypersensitivity reaction for patients undergoing surgical procedures. Incidence of perioperative anaphylaxis varies across countries, but studies have shown it ranges from 1:1250 to 1:18600 during surgeries using anesthesia.[1,2] Perioperative anaphylaxis can be lethal due to an acute immune response to an offending agent that affects multiple organ systems, requiring immediate medical attention.[3] The agents most commonly associated with these adverse events are usually neuromuscular blocking agents (NMBA), latex, and antibiotics.[4] Over the past decade, there has been an increasing number of reports of anaphylaxis induced by another anesthetic agent sugammadex.[5,6]

Sugammadex is the first selective relaxant binding agent (SRBA) approved by the FDA in 2015.[7] It reverses

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the neuromuscular blockade caused by NMBAs, such as rocuronium and vecuronium, which are used as muscle relaxers during surgeries. It acts by encapsulating the NMBA to form a stable complex, thus inactivating it.[8] Compared to previous agents used to reverse muscle relaxers, sugammadex has fewer muscarinic side effects and can reverse deep muscle relaxation in a dose-dependent manner, which makes it an appealing agent to use.[9] It has also has been used to attenuate anaphylactic reactions caused by rocuronium.[10]

Sugammadex, however, may carry its own risk of drug hypersensitivity reactions, defined as the "unintended and unwanted stimulation of immune or inflammatory cells by a medication,"[11] including the risk of anaphylaxis. Recently, there have been safety concerns that sugammadex might induce hypersensitivity and potentially fatal outcomes in various patient populations.[5,6] Previous systematic reviews have looked to identify and characterize cases of hypersensitivity associated with sugammadex.[12] However, hypersensitivity reactions range from mild cases requiring no treatment, to severe potentially fatal cases, such as perioperative anaphylaxis, that require immediate medical attention. There are currently no reviews that parse out the association of sugammadex with the more serious and life-threatening reaction of perioperative anaphylaxis. Therefore, we aimed to evaluate the association between sugammadex use and the incidence of anaphylaxis by summarizing the incidence rate of anaphylaxis events and reporting typical clinical presentation.

Material and Methods

Queries through PubMed, EMBASE, and Web of Science were conducted using the terms 'sugammadex AND (anaphyl* OR allerg* OR hypersensitiv*)' from inception to March 9, 2020. No filters were applied with regards to text availability, article type, publication date, or other customizable options. Duplicates were excluded.

Studies were selected if they met the following inclusion criteria: (1) the manuscript was available in English; (2) the article was a primary study (case report, case series, retrospective analysis, prospective/observational study, randomized control trial); (3) sugammadex was the most probable cause of the anaphylactic reaction; (4) the dose of sugammadex and description of the type of anaphylactic reaction was given; and (5) if the manuscript was a case report or series, the patient (s) needed to fit the diagnostic criteria of anaphylaxis as defined by the World Allergy Organization, which includes signs of any one of the following: (a) sudden (minutes to hours) onset of an illness with the involvement of the skin or mucosal tissue AND sudden respiratory symptoms or reduced blood pressure (BP) or signs of end organ dysfunction; (b) two of the following occurring suddenly after exposure to a likely allergen: skin/mucosal symptoms, respiratory symptoms, reduced BP, gastrointestinal symptoms; (c) sudden reduced BP after exposure to a known allergen: systolic BP <90 in adults or systolic BP <30% of baseline BP in adults/children.

Two independent reviewers were used during the screening, selection, and data extraction steps. A third reviewer would adjudicate any discrepancies. Unique titles were screened based on the title and abstract. The remaining articles were then retrieved, and full manuscripts were then screened based on the aforementioned inclusion factors. The selected publications were then reviewed, and data extraction was done using a standardized form. Among case reports, the Naranjo scale was used to rate the probability of sugammadex as the likely culprit for the anaphylactic reaction.[13]

Results

A total of 537 citations were identified from all sources. There were 224 duplicates removed, resulting in 313 unique titles. After reviewing the titles and abstracts, there were 73 articles remaining that were then evaluated based on the inclusion and exclusion criteria. After a full review, 24 articles were included in this review for data extraction [Figure 1].

Randomized controlled trials

The results of three randomized, double-blind, placebo-controlled studies were evaluated [Table 1].[14-16] Min *et al.*[14] and de Kam *et al.*[15] performed phase I clinical trial studies aimed to identify incident cases of hypersensitivity, including anaphylaxis, due to sugammadex among healthy non-anesthetized subjects. Both studies were multicenter randomized clinical trials and divided their subjects into one of three groups: Placebo, 4 mg kg^{-1}, or 16 mg kg^{-1} of sugammadex. Min *et al.*[14] defined anaphylaxis using the Sampson criteria 1,[17] while Kam *et al.*[15] also included the Brighton criteria.[18] Both studies utilized an adjudication committee to assess anaphylaxis. For Min *et al.*[14]only one patient (from the 16 mg kg^{-1} group) was determined to have had an anaphylactic reaction, with symptoms that included edema, swelling of the uvula, and a decrease in their peak expiratory flow. The patient was treated with antihistamines and corticosteroids, resulting in a resolution of their symptoms. There were no cases of anaphylaxis in the 4 mg kg^{-1} group, and the authors assumed that there is no dose-dependent occurrence of anaphylaxis. The authors report the incidence of sugammadex anaphylaxis as 0.33% (1 in 299). In Kam *et al.*'s study,[15] there were 488 healthy volunteers across four different countries, with 148 healthy subjects in the 4 mg kg^{-1}

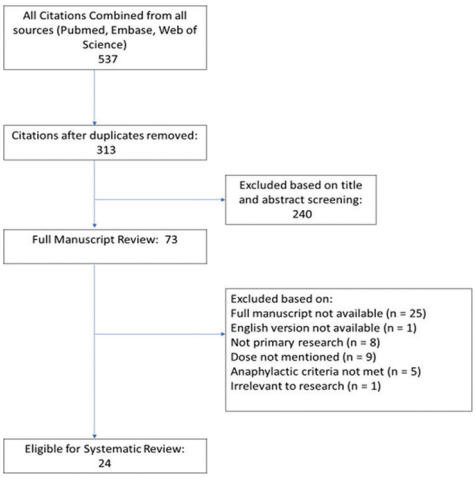

Figure 1: Consort diagram

group and 150 in the 16 mg kg^{-1} group. One patient met the diagnostic criteria for anaphylaxis according to both the Sampson and Brighton criteria, and two patients met the diagnostic criteria only according to the Brighton criteria. However, the authors reported protocol deviations at multiple sites (e.g. regarding which staff members performed safety assessments) which may have introduced bias in the reporting of anaphylactic reactions. All three patients were part of the 16 mg kg^{-1} treatment arm. Aside from the positive skin test for the first anaphylactic patients who met both the Sampson and Brighton criteria, all confirmatory tests for anaphylaxis were negative or within normal ranges.

Peeters *et al.*[16] evaluated the safety, tolerability, and pharmacokinetics of sugammadex using single high doses in 13 healthy adult subjects. They received 32, 64, and 96 mg kg^{-1}. One subject was reported as exhibiting more serious adverse events attributed to the first experimental dosage of sugammadex. Intracutaneous testing was performed to evaluate hypersensitivity and it resulted in a positive test suggesting a hypersensitivity reaction was probable, but it was not reported as anaphylaxis. Symptoms included tachycardia, paranesthesia in the skin of hands and face, moderate intensity of blurred vision, dysgeusia, nausea, and stomach discomfort. All adverse events in this study were resolved without implementing a treatment.

Observational studies

Two retrospective observational studies were identified, both of which were conducted in Japan [Table 1].[19,20] Miyazaki *et al.*[19] conducted a single-center retrospective observational study to investigate the incidence of sugammadex-induced anaphylaxis. All surgical cases attended by the center's anesthesiologists were evaluated from September 2012 to August 2015. Anaphylaxis was defined according to the World Allergy Organization guidelines (i.e. Sampson criteria).[21] There were 23,608 cases evaluated, with 15,479 patients who received sugammadex of which 6 (0.04%) cases of anaphylaxis were identified. The authors did not have a comparison group. Five of the six patients did not have any previous exposure to sugammadex, and only one patient reported any history of allergies (i.e., latex). The onset of symptoms ranged from < 1 minute to 4 min, with all patients requiring treatment for symptom resolution. Only one patient received a diagnostic test to confirm sugammadex as the causative agent.

Orihara *et al.*[20] conducted a multicenter retrospective observational study across four Japanese hospitals. The study compared the incidence of both hypersensitivity and anaphylaxis reactions between sugammadex and neostigmine. Anaphylaxis was defined in an unconventional way, which included at least two of the following: (1) a clinical score suggesting clinical hypersensitivity, (2) positive skins or basophil activation tests (BATs), and (3) elevated histamine or tryptase blood samples. The study evaluated 45,532 surgical cases requiring general anesthesia between January 2012 and December 2016. There were 29,962 patients who received sugammadex, with 6 cases of suspected sugammadex-induced anaphylaxis, resulting in an incidence rate of 0.02%. There were no cases of neostigmine-induced anaphylaxis. Of the six cases associated with sugammadex, only one of the six had previous exposure to sugammadex, and the onset of the reaction occurred in less than 8 min. All patients had a positive diagnostic test (i.e., skin tests for sugammadex as the causative agent for the anaphylactic reaction). All cases of anaphylaxis resolved upon appropriate treatment (e.g., epinephrine, antihistamine, steroid) with no fatalities reported.

Case reports

There were 14 case reports and 5 case series of sugammadex-induced anaphylaxis, which allowed for data extraction of 28 individual patient cases [Table 2].[22-40] Because 3 patient cases did not meet the World Allergy Organization criteria for anaphylaxis,[21,32,33,39] only results from 25 patient cases were included in the final data tables. The age of patients ranged from 3 to 89 years old and was split between 13 males and 12 females. Japan was the largest source of case reports, with 44% (11/25) of all case reports coming from Japanese hospital systems.[23,24,26,31,35,38,39] The number of reports from Japan may be due to higher usage frequency.[41] Concomitant medications were referenced for all but two cases.[33] The most common concomitant medications were those used for induction and maintenance of anesthesia. Medications used for supportive care were also included in the following: eight cases included antibiotics[24-26,30,32,34,36] and four cases mentioned benzodiazepine use for pre-operative

Table 1: Population studies (randomized controlled trials and observational studies)

Article	Study Design	Country	Study Population	Study Objective	Definition of Anaphylactic Reaction	Treatment Dose	Objective confirmation used	Number who received sugammadex	Number of anaphylaxis reaction	Incidence (95% CI)	Notes
Min *et al.*, 2018[14]	Randomized, double-blind placebo-controlled (January-July 2014)	USA and Belgium	Healthy, non-anesthetized adults 18-55 years old (*n*=299)	Assess the potential for hypersensitivity and anaphylaxis after initial and repeated exposure to SUG	World Allergy Organization Guidelines (Sampson criteria 1)	Placebo, 4 mg/kg, and 16 mg/kg	anti-SUG antibodies and serum tryptase	4 mg/kg: 151 16 mg/kg: 148	1	0.33%	Authors assumed there that incidence of anaphylaxis was not dose related
de Kam *et al.*, 2018[15]	Randomized, double-blind placebo-controlled (Aug 2009-Apr 2010)	Germany, The Netherlands, UK, and USA	Healthy non-pregnant, non-breastfeeding, non-anesthetized adults 18-55 years old (*n*=298)	Better understand signs of hypersensitivity due to SUG at the time of initial and repeated exposure relative to placebo	World Allergy Organization Guidelines (Sampson criteria 1) and Brighton Criteria	Placebo, 4 mg/kg, and 16 mg/kg	anti-SUG antibodies, serum tryptase, skin test (i.e., skin-prick and intradermal), basophil histamine release	4 mg/kg: 148 16 mg/kg: 150	3 (1 met Sampson and Brighton criteria, while 2 only met Brighton)	not reported	Assuming not dose related, the incidence would be 3/290=1.01%
Peeters *et al.*, 2010[16]	Randomized, double-blind, crossover, placebo-controlled (July 2008)	The Netherlands (single center)	Healthy non-pregnant, non-anesthetized adults 18-65 years old (*n*=13)	Evaluate the safety, tolerability, and pharmacokinetics of high-dose SUG (32-96 mg/kg)	Anaphylactic criteria not specified	32, 64, and 96 mg/kg bolus	serum tryptase and skin test (not specified)	12 subjects received all; 1 received only 32 mg/kg	0	not applicable	
Miyazaki *et al.*, 2018[19]	Retrospective single-center observational study (Sep 2012-Aug 2015)	Japan	All surgical cases attended by anesthesiologists (*n*=15,479)	Investigate the incidence of anaphylaxis caused by SUG	World Allergy Organization Guidelines	100 mg - 200 mg (reported only for anaphylaxis reaction)	serum tryptase	15,479	6	0.04% (95% CI, 0.014-0.084%)	
Orihara *et al.*, 2020[20]	Retrospective multicenter retrospective study (Jan 2012-Dec 2016)	Japan	Reviewed all consecutive cases of general anesthesia in four Japanese hospitals (*n*=49,532)	Compared the incidence of anaphylaxis induced by SUG vs. neostigmine	Met 2+ of following criteria: (i) clinical monitoring scoring suggesting immediate hypersensitivity reaction; (ii) positive skin tests or basophile activation tests to drugs during anesthesia; and (iii) elevated serum histamine or tryptase	80 mg - 200 mg (reported only for anaphylaxis reaction)	skin test (skin-prick), serum tryptase, serum histamine, basophil activation test	29,962	6	0.02% (95% CI: 0.007-0.044%)	concern about under-reporting and selection bias

SUG=sugammadex

Table 2: Case reports and case series

Article[a]	Type of publication	Country	Patient age (years)	Sex	Weight (kg)	History of Allergies	Sugammadex Dosage (mg/kg) or Dose (mg)[b]	Time to Symptom Onset (min)	Description of Anaphylactic Reaction	Treatment for Anaphylactic Reaction	Biological laboratory values (ng/mL)[c]	Allergy Testsd	Naranjo Score
O'Donnell *et al.*, 2017[22]	Case report	UK	62	M	140	No	0.7 mg/kg	4	Hypotension, erythematous rash	Metaraminol, hydrocortisone, ephedrine, chlorphenamine, epinephrine	T[a]: 49.6	(+) SPT for SUG (+) IDT for SUG	6
Yoshida *et al.*, 2020[23]	Case report	Japan	50	F	79	-	2.5 mg/kg	1	Hypotension, bradycardia, ST depression, hypercapnia, decreased SpO_2	Atropine, adrenaline	-	-	6
Yamaoka *et al.*, 2017[24]	Case report	Japan	36	F	65	No	3.1 mg/kg	Immediate	Hypotension, flushing	Ephedrine, epinephrine, hydrocortisone, famotidine, chlorpheniramine	T: 21.5 H: 0.32	(+) SPT for SUG/ROC (-) SPT for SUG (-) IDT for SUG	5
Menendez-Ozcoidi *et al.*, 2011[25]	Case report	Spain	17	M	62	No	3.2 mg/kg	1	Erythema, edema, hypotension, tachycardia, decreased SpO_2, wheezing	Hydrocortisone, methylprednisolone, dexchlorpheniramine, salbutamol	T: 7.9 H: 3.1	(+) SPT for SUG	8
Yamada *et al.*, 2018[26]	Case series	Japan	65	M	-	No	1.5 mg/kg	8	Hypotension, edema, erythema, cyanosis, increased airway pressure	Ephedrine, phenylephrine, norepinephrine, methylprednisolone, chlorphenamine,	T: 82.6 H: 1.27	(+) BAT for SUG/ROC (+) BAT for SUG	6
			29	F	-	No	3.4 mg/kg	5	Hypotension, tachycardia, erythema	Ephedrine, phenylephrine, adrenaline, dexamethasone, famotidine, chlorphenamine	T: 4.8 H: 3.44	(+) BAT for SUG	6
Kim *et al.*, 2019[27]	Case report	South Korea	42	M	78	cat hair	2.5 mg/kg	>5	Erythema, hypotension, tachycardia, swelling of eyes, facial edema, wheezing	Phenylephrine, epinephrine, dexamethasone, chlorpheniramine	T: 46.9	(+) IDT for SUG/ROC (-) IDT for SUG	6
Choi *et al.*, 2019[28]	Case report	South Korea	60	M	64	No	3.3 mg/kg	3	Hypotension, tachycardia, urticaria	Ephedrine, phenylephrine, epinephrine, norepinephrine, methylprednisolone, hydrocortisone, pheniramine	T: 2.4	(+) IDT for SUG/ROC (+) IDT for SUG	6

Contd...

Table 2: Contd...

Article[a]	Type of publication	Country	Patient age (years)	Sex	Weight (kg)	History of Allergies	Sugammadex Dosage (mg/kg) or Dose (mg)[b]	Time to Symptom Onset (min)	Description of Anaphylactic Reaction	Treatment for Anaphylactic Reaction	Biological laboratory values (ng/mL)[c]	Allergy Testsd	Naranjo Score
Escher, Cohen. 2019[29]	Case report	USA	67	F	115	Benazepril, ezetimibe, simvastatin, triamterene	3.5 mg/kg	1	Hypotension, decreased SpO_2, maculopapular rash	Phenylephrine, epinephrine, vasopressin, diphenhydramine, famotidine	T: 62	-	6
Bedirli *et al.*, 2018[30]	Case report	Turkey	22	F	85	vitamin B	4.0 mg/kg	Immediate	Hypotension, bradycardia, flushing, wheezing, decreased SpO_2, arrhythmia, increased airway pressure	Ephedrine, epinephrine, lidocaine, methylprednisolone, famotidine, pheniramine, norepinephrine	T: 7.6	-	5
Asahi *et al.*, 2012[31]	Case report	Japan	7	M	12	No	3.3 mg/kg	3	Paradoxical respiration, high pitched respiratory sounds, decreased SpO_2, wheals	Adrenaline, hydrocortisone	-	-	5
Sadleir *et al.*, 2014[32]	Case series	Australia	29	F	100	No	2.0 mg/kg	3	Hypotension, tachycardia, reduced cardiac output, edema	Metaraminol, adrenaline, phenylephrine	T: 59	(+) IDT for SUG (-) IDT for SUG/ROC	9
			15	F	-	Peanut butter	100 mg[e]	Within min	Rash, facial swelling, hypotension	Adrenaline, hydrocortisone, promethazine	T: 4.1	(+) IDT for SUG	9
Ue, 2016[33]	Case series	UK	50	M	-	-	200 mg	-	Hypotension, tachycardia, decreased SpO_2, urticaria	Adrenaline, chlorphenamine, hydrocortisone	T: 81	(+) SPT for SUG (+) IDT for SUG	9
			63	M	-	-	100 mg	-	Hypotension, tachycardia, decreased SpO_2, urticaria	Adrenaline, chlorphenamine, hydrocortisone	T: 36	(-) SPT for SUG (+) IDT for SUG	8
Colak *et al.*, 2018[40]	Case report	Turkey	3	M	15	No	2.0 mg/kg	After administration	Increased airway pressure, decreased SpO_2, wheezing, tachycardia, hypotension	Methylprednisolone, theophylline, pheniramine	-	-	4
Yoo *et al.*, 2016[34]	Case report	South Korea	35	M	109	animal hair	1.8 mg/kg	2	Erythematous wheal, hypotension, tachycardia, wheezing, decreased SpO_2	Dexamethasone, dexchlorpheniramine, salbutamol, epinephrine	-	(+) SPT for SUG	5
Takazawa *et al.*, 2014[35]	Case series	Japan	13	M	40	No	2.0 mg/kg	Shortly after administration	Facial swelling, hypotension, tachycardia, hypercapnia	Hydrocortisone, adrenaline, aminophylline	-	(+) SPT for SUG	5

Contd...

Table 2: Contd...

Article[a]	Type of publication	Country	Patient age (years)	Sex	Weight (kg)	History of Allergies	Sugammadex Dosage (mg/kg) or Dose (mg)[b]	Time to Symptom Onset (min)	Description of Anaphylactic Reaction	Treatment for Anaphylactic Reaction	Biological laboratory values (ng/mL)[c]	Allergy Testsd	Naranjo Score
			75	F	71	No	2.8 mg/kg	3	Hypotension, thoracic erythema	Adrenaline, chlorpheniramine, ranitidine, hydrocortisone, phenylephrine	-	(+) IDT for SUG	5
Ho *et al.*, 2016[36]	Case report	Australia	50	M	95	No	2.1 mg/kg	Shortly after administration	Hypotension, bradycardia, decreased SpO_2, periorbital swelling	Metaraminol, adrenaline, hydrocortisone	T: 60	(+) IDT for SUG/ROC (-) IDT for SUG	5
			34	M	62	No	3.2 mg/kg	1	Erythema, hypotension	Ephedrine, chlorpheniramine, ranitidine	-	(+) IDT for SUG	5
Frenkel *et al.*, 2015[37]	Case report	Israel	67	F	-	2-	200 mg		Hypotension, tachycardia, erythema, urticaria, increased airway pressure, wheezing	Adrenaline, hydrocortisone, albuterol	-	-	4
Yanai *et al.*, 2020[38]	Case report	Japan	71	F	65	No	2.0 mg/kg	2	Hypotension, bradycardia, cardiac arrest, ST depression	Noradrenaline, methylprednisolone, nitroglycerin, nicorandil	T: 81.2	(+) SPT for SUG	7
Godai *et al.*, 2012[39]	Case series	Japan	52	F	54	No	1.9 mg/kg	3	Hypotension, decreased SpO_2, tachycardia, erythema, increased airway pressure	Epinephrine, norepinephrine, methylprednisolone	-	(+) SPT for SUG	5
			89	F	45	No	2.2 mg/kg	7	Wheezing, decreased SpO_2, tachycardia, erythema	Methylprednisolone, aminophylline, procaterol	-	-	4

BAT=basophil activation test, F=female, H=serum histamine, IDT=intradermal test, M=male, ROC=rocuronium, SPT=skin-prick test, SpO_2=peripheral oxygen saturation, SUG=sugammadex, T=serum tryptase. [a]Cases within case series were only included if they met the inclusion criteria. [b]When the report provided dose (mg) and patient weight (kg); the dose is provided as mg/kg. [c]Biological laboratory values included serum tryptase (T) and serum histamine (H) reported in nanogram per milliliter (ng/mL). [d]Allergy tests included basophil activation test (BAT, skin-prick tests (SPT) and intradermal test (IDT). [e]Weight of this specific patient was not provided

anxiety.[25,28,29,32] The dose of sugammadex administered ranged from 0.7 to 4 mg/kg. Time to onset of symptoms reported in 23 cases ranged from 0 (immediate) to 8 min,[26] with 87% (20/23) of the reported cases occurring within 5 min.[22-25,28-32,34-38,40]

The most common symptom reported was hypotension, which was present in 92% (23/25) of all cases,[22-30,32-38,40] followed by some form of erythema in 76% (19/25),[22,24-31,33,34,37,39] decreased oxygen saturation in 44% (11/25),[23,25,29-31,33,34,36,39,40] tachycardia in 40% (10/25),[25-28,32-35,37,39,40] swelling/edema in 28% (7/25),[25-27,32,35,36] and wheezing in 28% (7/25).[25,30,34,37,39,40] There were other signs of respiratory issues such as hypercapnia in two cases.[23,35] There were also two cases of bradycardia, which were associated with ST depression and arrhythmia.[30,36] No patients died as a result of anaphylaxis.

Eighteen of the cases incorporated allergy testing. Seven cases used intradermal (IDT), five cases used skin-prick (SPT), and four cases tested using IDT and SPT. Additionally, two cases conducted allergy testing using a BAT. All cases conducted tests to confirm sugammadex as the cause, while six cases also tested the sugammadex–rocuronium complex. Sugammadex was the causative agent in 83% (15/18) of all positive allergy tests.[22,25,26,28,32-35,39] Out of the six cases that tested for the complex, there were five instances where the sugammadex–rocuronium complex was determined as a causative agent.[24,26-28,36] Of these five, three tested negative for sugammadex alone. There were no cases where rocuronium alone or other concomitant medications produced positive allergy results.

Only 48% (12/25) of all the cases included a diagnostic laboratory measurement that confirmed anaphylaxis.[22,24-27,29,32,33,36,38] Ten cases did not measure or report any biological measurements.[23,31,34,35,37,39,40] Three cases reported normal laboratory values, although bloodwork was done 12 h post-event for one of these cases.[28] Serum tryptase was the most common laboratory measurement used to confirm the diagnosis, accounting for 10 of the 12 objectively confirmed anaphylactic reactions.[22,24,27,29,32,33,36,38] Elevated histamine levels were present for the remaining two cases.[25,26] Based on the Naranjo scores, the articles were determined as follows: 3 of the cases were possible adverse events, 19 were probable, and 3 were definite [Table 2].

Discussion

The aim of this study was to review and elucidate the association between sugammadex use and anaphylaxis in patients. Our review included randomized controlled trials, population-based studies, and case reports and series.

While randomized controlled trials provide the strongest evidence to evaluate signal detection, the primary focus of the randomized controlled trials included in this review was on identifying hypersensitivity reactions in general and not primarily on anaphylaxis. Additionally, these randomized controlled trials only included young, healthy volunteers, who were not undergoing anesthesia, which does not reflect the real-world application of sugammadex (e.g. non-healthy patients undergoing surgery) and partially weakens the quality of evidence. There was also inconsistency in or complete lack of anaphylaxis diagnostic definition, which makes determining and comparing the anaphylaxis rate difficult. Min *et al.*[14] defined anaphylaxis using Sampson criteria, while Kam *et al.*[15] used both Sampson and Brighton criteria, which were more inclusive leading to a higher incidence rate. Peeters *et al.*[16] did not report an established diagnostic criteria to identify and verify anaphylaxis occurrence.

While Min *et al.*[14] reports on sugammadex-induced anaphylaxis incidence (0.33%), the authors assumed there was no dose-dependent relationship and therefore pooled all recipients of sugammadex (e.g. 4 and 16 mg/kg) in the incidence calculation. Kam *et al.*[15] did not report on the incidence of anaphylaxis, which could be due to concerns of biased reporting of hypersensitivity reactions. For the purposes of this review, the authors calculated the incidence of Kam *et al.*'s[15] results using Min *et al.*'s[14] dose assumptions and found the incidence of anaphylaxis to be 1.01% (3/298 patients). However, the interpretation of this value should be done with caution given the study limitations. Possible sources of bias and areas of concern in these randomized controlled trials were noted using the Cochrane Risk of Bias tool for randomized trials (RoB 2) [Table 3].[42]

Two retrospective observational studies included in this review were both conducted in Japan and provided a more real-world patient population.[19,20] While the studies were able to include over 29,000 and 15,000 sugammadex-exposed patients in the multicenter and single-center studies, respectively, there may be generalizability issues since the studies were conducted only in Japan. In the 5-year multicenter study[19] and 3-year single-center study,[20] there was a 0.02 and 0.04% incidence of anaphylaxis induced by sugammadex, respectively. Orihara *et al.*[20] reported on various confirmatory tests beyond serum tryptase and skin tests (i.e. serum histamine and BAT). Since the exact mechanism of action by which sugammadex may induce anaphylaxis is not well understood, it is useful to test different immune mediator responses. The two studies did not appear to have an adjudication process for case inclusion,

and due to their retrospective design, may have missed certain cases of anaphylaxis leading to an underestimation in the true incidence of sugammadex-induced anaphylaxis. There were inconsistencies in how the two studies diagnosed anaphylaxis which makes it difficult to compare them directly. In addition, the Miyazaki study did not perform allergy testing on most of its patients to verify sugammadex as the causative agent, introducing the unlikely possibility that alternative agents were responsible for the reaction. Possible sources of bias and areas of concern for these observational studies were noted using the Cochrane Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool [Table 4].[43]

There were different anaphylactic diagnostic criteria used for the randomized controlled trials and observational studies which make it difficult to compare the incidence rates across study types. Furthermore, the study population may not be comparable as both observational studies were conducted in Japan only, and the randomized controlled trials were conducted in young non-anesthetized individuals. Therefore, it is difficult to compare the incidence rates across the randomized controlled trials and observational studies mentioned here. Case reports of anaphylaxis all had similar clinical manifestations, with the most common ones being hypotension, erythema, decreased oxygen saturation, tachycardia, swelling, and wheezing. All cases of anaphylaxis to sugammadex were confirmed via allergy tests (i.e., SPT, IDT, or BAT), and some also included laboratory values indicative of anaphylaxis (i.e., serum tryptase or histamine). These methods of confirming and diagnosing anaphylaxis match guideline recommendations,[44] assuring that the reports included in this review were true anaphylaxis cases. However, there was a lack of consistency in skin testing across the case reports. While the French Society for Anaesthesia and Intensive Care (SFAR) and the French Society of Allergology (SFA) guidelines recommend waiting until 4–6 weeks after the anaphylactic event to perform tests, there were a few case reports that mentioned testing sooner, possibly leading to false negatives[27,38] There were also a few that tested 3 or more months later, which may have also affected results according to skin testing recommendations.[22,39,45]

In addition to evaluating sugammadex as the causative agent, some studies also tested the sugammadex–rocuronium complex. As expected, sugammadex was the most common causative agent for a positive allergy test. However, there were instances where the complex also produced a positive allergy test result. All other anesthetic agents were ruled out. Since not all case reports tested the sugammadex-rocuronium complex, it is difficult to determine whether sugammadex itself or the complex was the actual cause of anaphylaxis. There are theories that sugammadex binding to the rocuronium causes structural and chemical alterations that expose different functional groups with more allergenic potential.[27] Perhaps studies that incorporate alternative NMBAs like vecuronium can shed more light on the influence sugammadex has on anaphylaxis. Alternatively, allergy tests may need to start incorporating the sugammadex–rocuronium complex in their diagnoses in order to better differentiate what the causative agent really is.

Another theory to explain the role of sugammadex in the anaphylaxis reaction is the storage condition of sugammadex. In one of the case studies, light-exposed sugammadex and its complex with rocuronium both produced a positive BAT result whereas light-naïve sugammadex produced a negative result.[26] It may be possible that light exposure causes denaturation that exposes certain groups of sugammadex with allergenic potential. However, further studies are needed to support that theory.

This review included several limitations. As seen previously, there are intrinsic limitations to the quality of the studies

Table 3: Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)

	Domain 1: Randomization process	Domain 2: Derivations from intended interventions	Domain 3: Missing outcome data	Domain 4: Measurement of outcomes	Domain 5: Selection of the reported result	RoB 2 Overall
Min *et al.*, 2018[14]	Low	Some concerns	Low	Some concerns	Low	Some concerns
De Kam *et al.*, 2018[15]	Low	Some concerns	Low	Some concerns	Low	Some concerns
Peeters *et al.*, 2010[16]	Low	Low	Low	Some concerns	Low	Some concerns

Table 4: Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I)

	Domain 1: Confounding	Domain 2: Selection	Domain 3: Classification of intervention	Domain 4: Deviation from interventions	Domain 5: Missing data	Domain 6: Measurement of outcomes	Domain 7: Selection of reported results	ROBINS-I overall
Miyazaki *et al.*, 2018[19]	Serious	Low	Low	No information	Moderate	Moderate	Low	Serious
Orihara *et al.*, 2020[20]	Moderate	Low	Low	No information	Moderate	Low	Low	Moderate

that were included in this review, namely the retrospective observational studies and case reports. Additionally, there may have been a bias in our selection methods. Although we attempted to remove selection bias using multiple reviewers, the third reviewer's decision had the most weight when adjudicating any discrepancies. However, given the multi-stepped review process in selecting, reviewing, and verifying the articles, we are assured that the appropriate and relevant articles were included.

Conclusion

Based on the findings of this review, there appears to be a rare, but serious, association between sugammadex administration and anaphylaxis that warrants immediate medical attention. Clinical presentation is very similar in most case reports. However, the true incidence and cause of the anaphylaxis reaction (i.e. sugammadex vs. rocuronium–sugammadex complex) has yet to be elucidated. There is still a need for larger population-based studies in multiple countries using standardized diagnostic criteria to more accurately determine the incidence of sugammadex-induced anaphylaxis.

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Conflicts of interest

There are no conflicts of interest.

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