

Review Article

Hypersensitivity associated with sugammadex administration: a systematic review

A. Tsur¹ and A. Kalansky²

1 Medical Intern, Soroka University Medical Center, Ben-Gurion University of the Negev, Be'er Sheva, Israel

2 Medical Student, Medical School for International Health, Ben-Gurion University of the Negev Faculty of Health Sciences in Collaboration with Columbia University Medical Center, Be'er Sheva, Israel

Summary

Sugammadex is a drug used to reverse neuromuscular blockade induced by rocuronium or vecuronium. It has not yet been approved by the Food and Drug Administration in the USA due to concerns regarding hypersensitivity. The objective of this review was to identify similarities in the presentation of hypersensitivity reactions to sugammadex. A comprehensive search was performed in PubMed, Scopus and Web of Science for cases reporting hypersensitivity reactions to sugammadex. In addition, we contacted regulatory agencies and the company marketing the drug for unpublished reports. Reports were included if they were in English, primary investigations, lacked an alternative probable explanation for the reaction and included a comprehensive description of the hypersensitivity. We identified 15 cases of hypersensitivity following sugammadex administration. All cases that reported exact timing (14/15) occurred in 4 min or less. Most of the patients (11/15; 73%) met World Anaphylaxis Organization criteria for anaphylaxis. Awareness must be raised for the possibility of drug-induced hypersensitivity during the critical 5-min period immediately following sugammadex administration.

Correspondence to: A. Tsur

Email: avishaitstur@gmail.com

Accepted: 13 April 2014

Introduction

Sugammadex is a gamma-cyclodextrin [1] used as the first selective neuromuscular blocking drug binding agent [2]. By encapsulating aminosteroids [3] such as rocuronium and vecuronium, it reverses the induced anaesthetic neuromuscular block in a mean time of < 2 min. It has rapid renal clearance [4], and the dosage is independent of age and fat distribution [5], and dependent only on patient weight and the depth of neuromuscular block [6].

It is a safe [7, 8], effective and important drug [9] that eliminates the need to use the combination of acetylcholinesterase inhibitors with antimuscarinic agents

[4]. It has been approved for use in over 70 countries [10]. However, the USA's Food and Drug Administration (FDA) has not yet approved sugammadex owing to concerns about its safety profile, especially the perceived risk of drug-induced, potentially life-threatening, hypersensitivity reactions. Our objective was to gather both published and unpublished cases, and to identify similarities in the presentation of hypersensitivity reactions associated with sugammadex administration.

Methods

PubMed, Scopus and Web of Science were searched for 'sugammadex AND (anaphylaxis OR hypersensitivity)'

in March 2014. No filters were applied, to find any available literature on the topic regardless of the year of publication, type of publication or journal. Furthermore, this search strategy returned electronic publications ahead of print, which could be important as sugammadex has only been recently introduced in most countries. In addition, we contacted Merck Sharp & Dohme, which markets sugammadex, the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), to seek unpublished reports.

Both authors independently screened the titles and abstracts, if available, of all results from the search. Full manuscripts of relevant reports were retrieved. The same reviewers independently assessed the full manuscripts using a set of eligibility criteria: (1) the study was written in English; (2) the study was a primary investigation/report (e.g. case report, surveillance study or a controlled trial); (3) the study did not include an alternative probable explanation for the reaction; and (4) the study included a comprehensive description of the dose of sugammadex given, the hypersensitivity reaction, the time to reaction and the treatment given. Any disagreement between the reviewers was discussed and resolved by consensus after a secondary review of the original article. A figure describing the selection process has been drawn according to the PRISMA statement [11].

The references of relevant articles were manually searched for additional suitable studies. If appropriate by title, the authors applied the same screening process using the eligibility criteria outlined earlier.

One review author (AT) extracted data from each case using a pre-structured table. The extracted information included, but was not limited to, type of publication, country, year of publication, age, weight, sex, history of allergies, history of exposure to sugammadex, surgical procedure for which anaesthesia was needed, induction medications, type and dosage of neuromuscular blocking drugs, maintenance drugs, dosage of sugammadex given, description of the hypersensitivity reaction, time to reaction, treatment given for the reaction, and results of a skin prick test or an intradermal test. We attempted to contact authors to complete missing data. We then performed a frequency analysis of relevant data.

Confirmation of the diagnosis using a skin prick test or an intradermal test were classified as positive, negative or not done [12]. Dosage of sugammadex was calculated where possible to match milligrams per kilogram using the given weight of the patient and the total dosage of sugammadex administered. We defined anaphylaxis according to the World Allergy Organization (WAO) criteria [13].

Results

Figure 1 demonstrates the review process. The database search of sugammadex yielded a total of 157 results. We were able to identify 26 records from other sources. After removal of duplicates, the remaining 99 records were screened independently. Title/abstract screening excluded 74 articles, many relating to the possible use of sugammadex as a treatment in cases of rocuronium anaphylaxis. Out of the 25 records, 14 failed to meet the inclusion criteria. Four were in Japanese [14–17]; three were not primary investigations [18–20]; in the six from the MHRA, sufficient detail of the hypersensitivity reaction could not be disclosed owing to concerns over patient confidentiality; and one included a probable alternative explanation for the reaction [21]. We identified a total of 11 studies to be included in the qualitative analysis, including: two case series of three patients each [22, 23]; six case reports [24–29]; an abstract [30]; and two clinical trials [7, 31]. Table 1 summarises all the included patients.

Table 2 summarises the key signs and symptoms associated with sugammadex hypersensitivity as found in the systematic review. The most frequently shared signs and symptoms were rash, hypotension and tachycardia in decreasing order of incidence. The WAO anaphylaxis criteria were met in more cases than any single sign or symptom besides rash. Importantly, all of the individuals recovered eventually. Out of 15 reports, 14 included an accurate time to the onset of reaction. The mean time was 1.9 min (1 min and 52 s), with the earliest during administration and the latest 4 min after receiving a dose of sugammadex. Of the 15 patients, only 11 underwent skin prick testing and/or intradermal testing (two patients refused: in one case the physician advised against testing; and in another case the reason

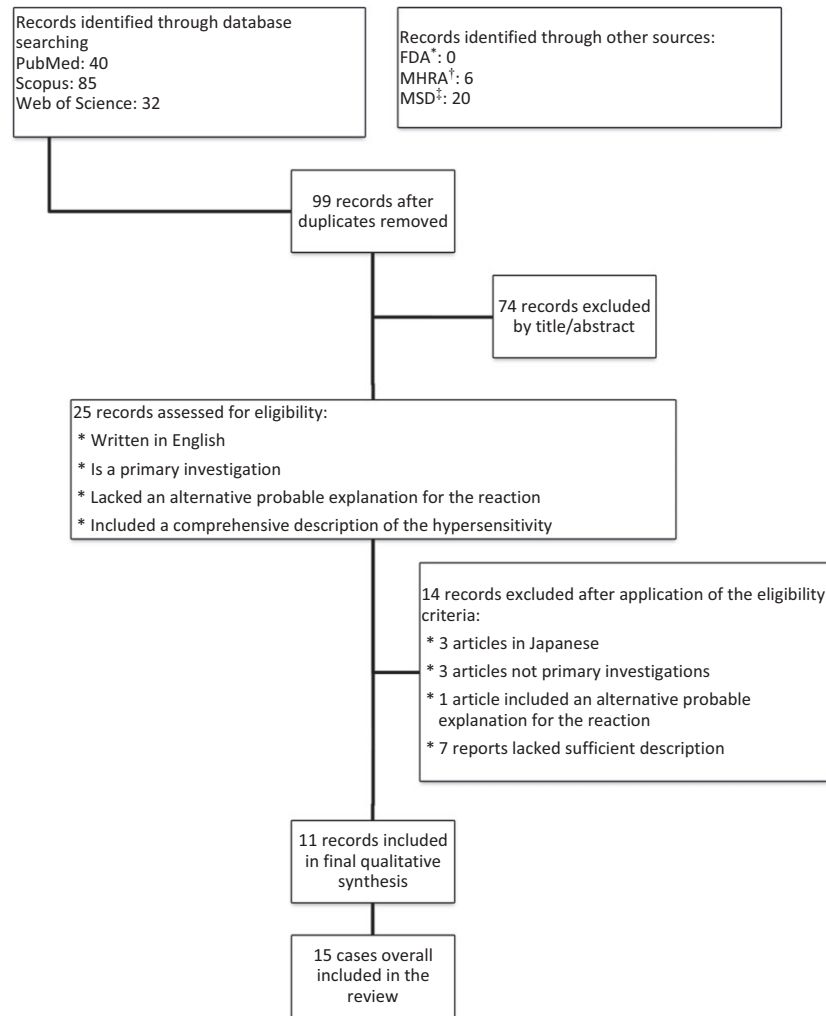


Figure 1 PRISMA flow diagram. *FDA, Food and Drug Administration; †MHRA, Medicines and Healthcare products Regulatory Agency; ‡MSD, Merck Sharp & Dohme.

remains unknown). Out of these 11, 10 had a positive confirmatory result.

There were two notable findings. First, in two of the cases, intradermal testing was performed using a mixture of sugammadex and rocuronium, which produced an attenuated reaction. Second, in 12 cases, it was explicitly reported that the patients had no previous exposure to sugammadex. In the remaining three cases, there were no data regarding previous exposure.

Discussion

As far as we know, this is the first systematic review of the literature regarding sugammadex-induced hypersensitivity. It includes all of the available published literature, literature pending publication and

unpublished reports written in English. Two reviewers independently screened, assessed and selected the reports that were included in the final qualitative analysis.

Our review identified a few important findings. Out of 11 patients who underwent confirmatory skin prick testing, 10 were proven to develop sugammadex-induced hypersensitivity. This seems to justify the concerns of the FDA regarding hypersensitivity. However, all of the individuals included in our review survived. The individual with the negative skin prick test also presented with a different set of symptoms. It was suspected that the individual did not suffer from sugammadex-induced hypersensitivity, yet no alternative probable explanation was suggested.

Table 1 Summary of patient data in hypersensitivity associated with sugammadex administration.

Article	Type of publication	Country	No.	Age; years	Weight; kg	Sex	History of allergies	Sugammadex dosage; mg.kg ⁻¹ except where dose given	Time to onset of reaction; min	Reaction	WAO criteria	Confirmation of hypersensitivity to sugammadex	Previous exposure to sugammadex
Peeters et al. (2010) [31]	Clinical trial	The Netherlands	1	18-65	–	M	No	8.4	0	Skin, head, and face parasthesia Blurred vision Dysguesia Nausea Tachycardia Stomach discomfort Skin flushing Abdominal erythematous rash	Yes	Positive	No
de Kam et al. (2010) [7]	Clinical trial	Germany	2	18-45	–	F	Not reported	32.0	1	Dysguesia Burning sensation Nausea Sensation of heaviness Agitation Abdominal cramps Skin rash at the infusion site and the right forearm	No	Negative	Not reported
Menendez-Ozcoidi et al. (2011) [24]	Case report	Spain	3	17	62	M	Inactive asthma House dust mite	3.2	1	Erythema anterior thorax Lip and palpebral oedema Hypotension S _p O ₂ 93% Tachycardia Bilateral wheeze	Yes	Positive	No
Chugo (2012) [30]	Abstract	Spain	4	26	70	M	Asthma House dust mite	2.9	1	Rash Wheezing Hypotension	Yes	Positive	No
Godai et al. (2012) [22]	Case series	Japan	5	41	53	F	No	1.9	3	Facial erythema Blepharodema Hypotension Tachycardia	No	Positive	No
			6	52	54	F	No	1.8	3	Generalised erythema S _p O ₂ 83% Wheezing on auscultation S _p O ₂ 91% Tachycardia Left arm erythema	Yes	Positive	No
			7	89	45	F	No	2.2	4		Yes	Not done	No

Table 1 (continued)

Article	Type of publication	Country	No.	Age; years	Weight; kg	Sex	History of allergies	Sugammadex dosage; mg.kg ⁻¹ except where dose given	Time to onset of reaction; min	Reaction	WAO criteria	Confirmation of hypersensitivity to sugammadex	Previous exposure to sugammadex
Asahi et al. (2012) [25]	Case report	Japan	8	7	12	M	No	3.3	3	High-pitched respiratory sounds Paradoxical respiration S _p O ₂ 82% Wheals on neck, chest, and upper extremities	Yes	Not done	No
Soria et al. (2012) [26]	Case report	France	9	62	65	M	Not reported	2.3	3	Erythema without oedema Hypotension Tachycardia S _p O ₂ 40%	Yes	Positive	Not reported
Tokuwaka et al. (2013) [27]	Case report	Japan	10	37	58	M	Shrimp and crab	2.0	1	Hypotension Tachycardia Itching anterior chest Wheals over entire body Lips and palpebral swelling	Yes	Not done	No
Mimaru et al. (2013) [29]	Case report	Japan	11	10	–	M	Asthma Cats House dust mite Pollen	200 mg	2	Hypotension S _p O ₂ 47% Wheezing Erythema of both legs, femoral region, and abdomen	Yes	Not done	Not reported
Jeyadoss et al. (2014) [28]	Case report	Australia	12	56	90	M	No	2.2	1	Hypotension Tachycardia	No	Positive	No
Sadleir et al. (2014) [23]	Case series	Australia	13	29	100	F	No	2.0	3	Generalised oedema Hypotension Tachycardia	Yes	Positive	No
			14	15	–	F	Peanut butter	100 mg	Within minutes	Face, arms, and trunk rash Facial swelling	Yes	Positive	No
			15	33	–	F	No	200 mg + 200 mg	0	Hypotension Bronchospasm S _p O ₂ 58%	No	Positive	No

WAO, World Allergy Organization.

Table 2 Signs and symptoms in hypersensitivity associated with sugammadex administration. Values are number (proportion).

Symptom/sign	Cases/total
Rash	12/15 (80%)
WAO anaphylaxis	11/15 (73%)
Positive SPT/IDT	10/11 (91%)
Hypotension	9/15 (60%)
Tachycardia	8/15 (53%)
Decreased S_pO_2	7/15 (47%)
Oedema	5/15 (33%)
Abnormal respiratory sounds	5/15 (33%)

WAO, World Allergy Organization; SPT, skin prick testing; IDT, intradermal testing.

Based on the consistencies in reaction time between the cases, we conclude that most, if not all, hypersensitivity reactions occur within 5 min of sugammadex administration. The immediacy and sequence of reactions, as well as the confirmation of the diagnosis using skin prick testing or intradermal testing, make it highly likely that they were associated with administration of sugammadex. Therefore, we suggest vigilance by the anaesthesia staff during this critical time period, as hypersensitivity reactions can be life threatening – especially in the presence of rash, WAO anaphylaxis criteria, hypotension, tachycardia or decreased S_pO_2 as found in 80%, 73%, 60%, 53% and 47% of our cases, respectively. This implies that the WAO anaphylaxis criteria may be a better diagnostic tool than individual signs and symptoms excluding rash.

It remains unknown why some of the patients with first exposure to sugammadex developed a hypersensitivity reaction. One possible explanation is that those individuals were sensitised by cyclodextrins found in foods. It has been estimated that the average person consumes approximately 4 g of gamma-cyclodextrins per day [32].

Our review has several limitations. First, as in any systematic review of predominantly case reports, we are limited in our ability to draw quantitative conclusions. This is due to insufficient assessment of validity, publication bias and selective reporting in case reports. We tried to mitigate this limitation by being conservative when drawing conclusions. Because of the extremely small number of cases reported in the English literature, it is not possible to base the review

on clinical trials only. Second, there are limited descriptive data about the patients included in the studies. For example, five patients were lacking anthropometric or age data, four individuals did not undergo skin prick testing and two cases lacked information regarding history of allergies. Additional data regarding co-morbidities and medical history are incomplete. Third, two reports including several additional cases were in Japanese, as well as a series of 10 case reports presented in the 31st Annual Meeting of the Japanese Society for Clinical Anesthesia [25].

In conclusion, sugammadex has been shown to be a safe [7, 8], effective [4] and an important drug [9] that can be used for the rapid reversal of neuromuscular blockade. However, awareness must be raised about the possibility of drug-induced hypersensitivity during the critical 5-min period immediately following administration, which, with prompt treatment, should be easier to manage and have a better prognosis than with delayed treatment.

Competing interest

No external funding and no competing interests declared.

References

- Booij LH. Cyclodextrins and the emergence of sugammadex. *Anaesthesia* 2009; **64**(Suppl. 1): 31–7.
- Schaller SJ, Fink H. Sugammadex as a reversal agent for neuromuscular block: an evidence-based review. *Core Evidence* 2013; **8**: 57–67.
- Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesthesia and Analgesia* 2007; **104**: 575–81.
- Yang LP, Keam SJ. Sugammadex: a review of its use in anaesthetic practice. *Drugs* 2009; **69**: 919–42.
- Sanfilippo M, Alessandri F, Shousha AA, Sabba A, Cutolo A. Sugammadex and ideal body weight in bariatric surgery. *Anesthesiology Research and Practice* 2013; **2013**: 389782.
- Mirakhor RK. Sugammadex in clinical practice. *Anaesthesia* 2009; **64**(Suppl 1): 45–54.
- de Kam PJ, van Kuijk J, Prohn M, Thomsen T, Peeters P. Effects of sugammadex doses up to 32 mg/kg alone or in combination with rocuronium or vecuronium on QTc prolongation. *Clinical Drug Investigation* 2010; **30**: 599–611.
- Dahl V, Pendeville PE, Hollmann MW, Heier T, Abels EA, Blobner M. Safety and efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in cardiac patients undergoing noncardiac surgery. *European Journal of Anaesthesiology* 2009; **26**: 874–84.
- Fuchs-Buder T, Meistelman C, Raft J. Sugammadex: clinical development and practical use. *Korean Journal of Anesthesiology* 2013; **65**: 495–500.

10. Woo T, Kim KS, Shim YH, et al. Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients. *Korean Journal of Anesthesiology* 2013; **65**: 501–7.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 2009; **339**: b2535.
12. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test – European standards. *Clinical and Translational Allergy* 2013; **3**: 3.
13. Simons FE, Arduzzo LR, Bilo MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organization Journal* 2011; **4**: 13–37.
14. Motoyama Y, Izuta S, Maekawa N, Chuma R. Case of anaphylactic reaction caused by sugammadex. *Masui* 2012; **61**: 746–8.
15. Ohshita N, Tsutsumi YM, Kasai A, et al. Two cases of anaphylactoid reaction after administration of sugammadex. *Masui* 2012; **61**: 1261–4.
16. Takahiro T, Haruyama N, Mae T, Doi K, Ozaki M. Be careful about anaphylactic shock by antagonism of the neuromuscular blockade~ cases of anaphylactic shock induced by sugammadex. *Critical Care Medicine* 2012; **40** (Suppl. 1): 1145.
17. Takazawa T, Tomita Y, Nagata C, Saito S. Three cases of suspected anaphylactic shock due to sugammadex. *Journal of the Japanese Society of Intensive Care Medicine* 2013; **20**: 71.
18. Chon JY. In the hour of Sugammadex. *Korean Journal of Anesthesiology* 2013; **64**: 3–5.
19. Malinovsky JM, Plaud B, Debaene B, Mertes PM. Do we know all indications and side effects of sugammadex? *Annales Françaises D'anesthésie et de Réanimation* 2011; **30**: 709–10.
20. Savic L, Savic S, Hopkins PM. Anaphylaxis to sugammadex. *Anaesthesia and Intensive Care* 2014; **42**: 7–9.
21. Amao R, Zornow MH, Cowan RM, Cheng DC, Morte JB, Allard MW. Use of sugammadex in patients with a history of pulmonary disease. *Journal of Clinical Anesthesia* 2012; **24**: 289–97.
22. Godai K, Hasegawa-Moriyama M, Kuniyoshi T, et al. Three cases of suspected sugammadex-induced hypersensitivity reactions. *British Journal of Anaesthesia* 2012; **109**: 216–8.
23. Sadleir PH, Russell T, Clarke RC, Maycock E, Platt PR. Intraoperative anaphylaxis to sugammadex and a protocol for intradermal skin testing. *Anaesthesia and Intensive Care* 2014; **42**: 93–6.
24. Menendez-Ozcoidi L, Ortiz-Gomez JR, Olaguibel-Ribero JM, Salvador-Bravo MJ. Allergy to low dose sugammadex. *Anaesthesia* 2011; **66**: 217–9.
25. Asahi Y, Omichi S, Adachi S, Kagamiuchi H, Kotani J. Hypersensitivity reaction probably induced by sugammadex. *Acta Anaesthesiologica Taiwanica* 2012; **50**: 183–4.
26. Soria A, Motamed C, Gaouar H, Chemam S, Amsler E, Frances C. Severe reaction following sugammadex injection: hypersensitivity? *Journal of Investigative Allergology and Clinical Immunology* 2012; **22**: 382.
27. Tokuwaka J, Takahashi S, Tanaka M. Anaphylaxis after sugammadex administration. *Canadian Journal of Anesthesia* 2013; **60**: 733–4.
28. Jeyadoss J, Kuruppu P, Nanjappa N, Van Wijk R. Sugammadex hypersensitivity – a case of anaphylaxis. *Anaesthesia and Intensive Care* 2014; **42**: 89–92.
29. Mimaru K, Gotoh K, Fujiwara K, Nakamura A, Nishimura A, Iijima T. A case report of anaphylaxis associated with sugammadex administration in a pediatric oral surgical case. *Journal of Japanese Dental Society of Anesthesiology* 2013; **41**: 199–200.
30. Chugo S. Allied health: anaphylaxis after anesthetic reversal. *World Allergy Organization Journal* 2012; **5**(Suppl. 2): S78.
31. Peeters PA, van den Heuvel MW, van Heumen E, et al. Safety, tolerability and pharmacokinetics of sugammadex using single high doses (up to 96 mg/kg) in healthy adult subjects: a randomized, double-blind, crossover, placebo-controlled, single-centre study. *Clinical Drug Investigation* 2010; **30**: 867–74.
32. Munro IC, Newberne PM, Young VR, Bar A. Safety assessment of gamma-cyclodextrin. *Regulatory Toxicology and Pharmacology* 2004; **39**(Suppl. 1): S3–13.