

Incidence of Anaphylaxis to Sugammadex in a Single-Center Cohort of 19,821 Patients

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See Article, p 93

BACKGROUND: Sugammadex is a modified cyclodextrin that is being increasingly used in anesthetic practice worldwide for the reversal of the aminosteroid neuromuscular blockers rocuronium and vecuronium. Its safety profile, however, is incompletely understood. One such aspect is the incidence of anaphylactic reactions that occur after its administration. While several case reports exist in the literature, there is a paucity of information on the actual incidence of anaphylactic reactions.

METHODS: A single-center retrospective chart review identified patients who experienced anaphylaxis to sugammadex in the institutional electronic medical record system. These charts were then reviewed to determine whether the etiology of anaphylaxis was sugammadex administration.

RESULTS: Two patients experienced anaphylaxis to sugammadex, which occurred in a single institution cohort of 19,821 patients who received 23,446 total doses. This rate is markedly lower than the 1/300 that the manufacturer's package insert states and also lower than the 1/2500 that the only other large cohort study performed has reported.

CONCLUSIONS: The incidence of anaphylaxis to sugammadex in this cohort of patients was 2 of 19,821 patients, who received a total of 23,446 doses. (Anesth Analg 2021;132:93-7)

KEY POINTS

- **Question:** What is the incidence of anaphylactic reaction to sugammadex?
- **Findings:** Two patients experienced an anaphylactic reaction to sugammadex in a group of 19,821 patients who received 23,445 total doses.
- **Meaning:** This retrospective analysis found a low risk of anaphylaxis of approximately 1 of 10,000.

GLOSSARY

EMR = electronic medical record; **FDA** = Food and Drug Administration; **IRB** = institutional research board; **IV** = intravenous; **JSA** = Japanese Society of Anesthesiologists; **MAP** = mean arterial pressure; **WAO** = World Allergy Organization

Sugammadex is a modified cyclodextrin that has become available in clinical anesthesiology practice to rapidly reverse the aminosteroid neuromuscular blocking drugs rocuronium and vecuronium. It was approved by the Food and Drug Administration (FDA) for clinical use in the United States in 2015, although it has been available in other countries since 2008.¹ It possesses several favorable properties, including more rapid onset of action and a reversal of paralysis that is more complete than

traditional neuromuscular blocker reversal agents. For these reasons, its use will continue to increase as its availability increases in the United States.²

The safety profile of this drug is, however, poorly described.³ One aspect of safety information that is uncertain is the incidence of anaphylactic reactions that occur after its administration. According to the manufacturer's package insert,⁴ the rate of anaphylaxis is 0.3%, which was based on a single study with a sample size of only 299 participants. There are numerous published case reports of hypersensitivity reactions and anaphylactic reactions to sugammadex, but it is not possible to accurately estimate the incidence given the scattered nature of these incidents.^{5,6} To date, only a single large cohort of patients at a single institution in Japan⁷ has been investigated to determine an accurate rate of anaphylactic reactions and placed the incidence at 0.039% or approximately 1 of 2500. This study, however, had several limitations, including identifying anaphylactic reactions utilizing a voluntary self-report

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system and being in a different geographical region where rates of anaphylaxis to sugammadex could have regional variation.

This study aimed to identify the incidence of anaphylaxis to sugammadex at a single, large-volume tertiary care center in the United States to aid in providing additional information on the rate of allergic reactions.

METHODS

This study was approved and the need for written consent by subjects waived by the institutional research board (IRB) of the Stanford University School of Medicine (IRB number: 43677). The dates of inclusion of patient charts for analysis were between January 2016 and January 2019.

Using the Stanford University clinical research database, 2 parallel independent electronic searches were simultaneously performed. The first search was performed to identify patients within the institutional electronic medical record (EMR) database (Epic Systems, Madison, WI) of 3,967,285 patients who were manually flagged with a drug allergy to sugammadex. Physicians and nurses may perform manual entry of allergies into this EMR. Two charts were identified as having an anaphylactic reaction to sugammadex. A chart review of these patients was then performed to evaluate the reaction according to the World Allergy Organization (WAO) guidelines for the Assessment and Management of Anaphylaxis diagnostic criteria displayed in Figure 1.

The second search was performed to capture any patient(s) who experienced an anaphylactic reaction to sugammadex but who may not have had their chart manually flagged with a drug allergy. The search was, again, undertaken to incorporate all 3,967,285 patients in the institutional EMR, but the search criteria identified any charts where sugammadex and epinephrine, by intravenous (IV) bolus or infusion, were administered within the same anesthetic record. Epinephrine coadministration was chosen because it is the first-line treatment for anaphylaxis and could, therefore, narrow down the manual chart review. Sugammadex was administered in 19,821 unique anesthetic records for 23,446 total doses, and sugammadex and epinephrine were administered together in 779 anesthetic records. The 779 anesthetic records were then manually reviewed by the author (M.A.B.), including all intraoperative vital signs, ventilator data, medications administered by the anesthesiologists, and all clinical notes made by the anesthesiologists and surgeons. Two patients were confirmed as having suffered an anaphylactic reaction to sugammadex. Again, the WAO guidelines for the Assessment and Management of Anaphylaxis diagnostic criteria were used for evaluation, as shown in Figure 1.

For reversal of neuromuscular blockade, anesthesiologists at our institution administer either

sugammadex or neostigmine at their clinical discretion, and both medications are routinely available in the anesthesia drug cart.

RESULTS

In the time period studied, a total of 23,446 doses of sugammadex were administered to 19,821 different patients. Of the total doses of sugammadex, 23,211 received rocuronium and 235 received vecuronium as the paralytic during the case. Neostigmine was utilized for neuromuscular blockade 2918 times during the study period. The number of patients who did not have a reversal agent charted in the study period was 289.

Two patients in each of the parallel, independent searches exhibited an anaphylactic reaction. The same 2 patients were identified in each parallel search. The rate of anaphylactic reaction to sugammadex in this single-institution cohort, therefore, was 2 of 23,446 (0.00852% [95% confidence interval, 0.00103–0.03078]) doses in 19,821 (0.01009% [95% confidence interval, 0.00122–0.03644]) different patients. Confidence intervals were calculated using the Clopper–Pearson method for calculating the 95% confidence interval of a proportion. The search algorithm and results are summarized in Figure 2.

The first patient was an 81-year-old African American female (162 cm tall, 75.5 kg) who underwent microwave ablation of a right kidney mass under general anesthesia. Her medical history consisted of right renal cell carcinoma, atrial fibrillation, essential hypertension, and type 2 diabetes mellitus. She had no known drug allergies. She had received general anesthetics in the past but had no prior exposure to sugammadex. At the conclusion of surgery, 139.8 mg sugammadex IV was administered, and 1 minute later significant hypotension resulted (from 126/76 to 58/36 mm Hg), tachycardia (from 56 to 99 beats/min), and peak airway pressure (from 18 to 36 cm H₂O) occurred. No cutaneous erythema was noted. Initial resuscitation efforts were made with 20 mg ephedrine IV and 200 µg phenylephrine IV, but with no improvement in mean arterial pressure (MAP), a dose of 75 µg epinephrine IV was administered, which did not improve the MAP, but subsequent boluses of 500 µg every 4 minutes for 4 total doses resulted in a time to achieve hemodynamic stability of 19 minutes. Other medications administered included 100 mg hydrocortisone IV. The patient suffered no adverse neurological or cardiorespiratory consequences. Tryptase levels were not drawn, and no subsequent allergy testing was performed. This case meets WAO (Figure 1) diagnostic criteria because this patient experienced reduced blood pressure and respiratory compromise (increased airway pressure) after sugammadex administration. Medications which

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg: generalized urticarial, itching, or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
 - A) Respiratory compromise (eg: dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - B) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg: hypotonia, collapse, syncope, incontinence) OR
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - A) Involvement of the skin-mucosal tissue (eg: generalized urticarial, itch-flush, swollen lips-tongue-uvula)
 - B) Respiratory compromise (eg: dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - C) Reduced blood pressure or associated symptoms (eg: hypotonia, collapse, syncope, incontinence)
 - D) Persistent gastrointestinal symptoms (eg: crampy abdominal pain, vomiting) OR
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
 - A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
 - B) Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

Figure 1. World Allergy Organization guidelines for the Assessment and Management of Anaphylaxis, clinical criteria for diagnosing anaphylaxis.

had been administered in the preceding 30 minutes before sugammadex administration were propofol IV infusion (125 µg/kg/min), remifentanyl IV infusion (0.1 µg/kg/min), phenylephrine IV (boluses of 150 and 100 µg), 1000 mg acetaminophen IV, and 4 mg ondansetron IV.

The second patient was a 47-year-old Caucasian male (163 cm tall, 87 kg) who underwent a transsphenoidal resection of a nonsecreting pituitary adenoma under general anesthesia. The patient had no known drug allergies and a history of essential hypertension. His surgical history consisted of wisdom teeth extractions and a cystectomy, with no previous exposure to sugammadex. At the conclusion of surgery, 200 mg

sugammadex IV was administered, and 2 minutes later, hypotension (from 125/65 to 47/28 mm Hg) and tachycardia (from 61 to 105 beats/min) occurred. Peak airway pressure did not increase. A full-body rash was noted within 5 minutes of the sugammadex administration. Initial efforts to achieve hemodynamic stability consisted of 3 boluses of 150 µg phenylephrine IV, a single bolus of 10 mg ephedrine IV, and 1 unit vasopressin IV with no significant improvement in MAP. Ten repeated boluses of 10 µg epinephrine IV were given over the next 30 minutes. Fifty milligrams diphenhydramine IV, 40 mg famotidine IV, and 100 mg hydrocortisone IV were also administered. The total time to achieve hemodynamic stability was 17

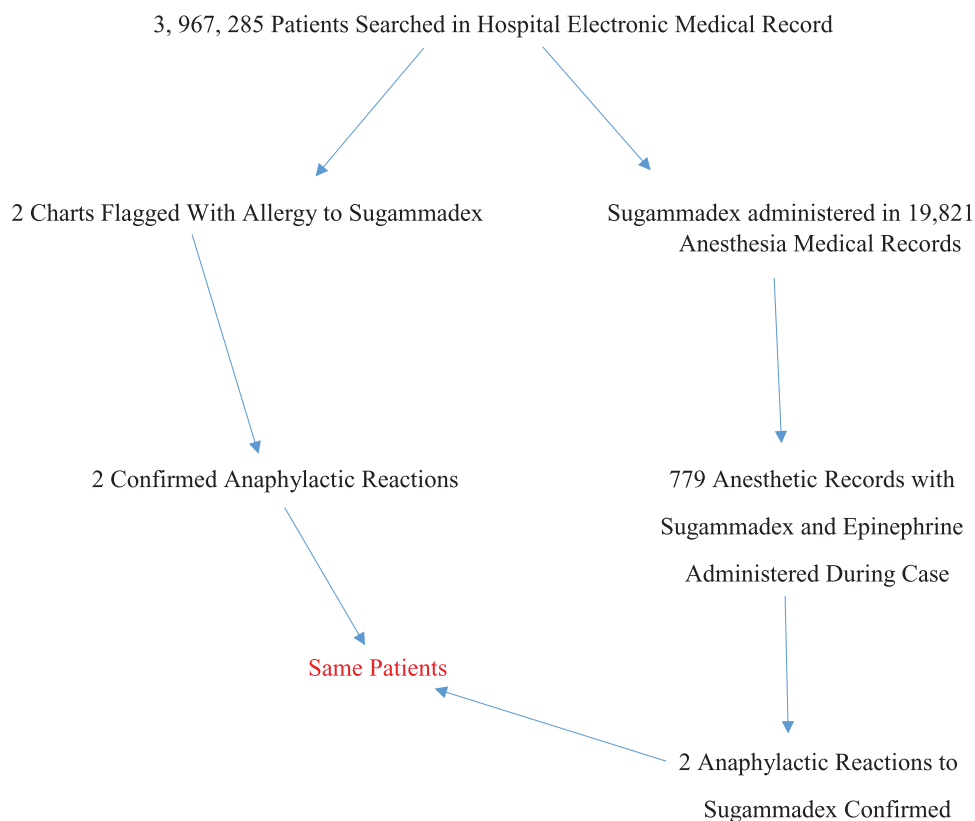


Figure 2. Institutional electronic medical records search algorithm.

minutes. The patient suffered no adverse neurological or cardiorespiratory consequences. No tryptase levels were drawn, and no allergy testing was subsequently performed. This case meets WAO (Figure 1) diagnostic criteria because this patient experienced involvement of skin-mucosal tissue (generalized urticaria) and reduced blood pressure after sugammadex administration. Medications that had been administered in the preceding 30 minutes before sugammadex administration were sevoflurane (0.8%) and a 100- μ g phenylephrine IV bolus.

DISCUSSION

Anaphylaxis is defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death.”⁸ Common triggers in the perioperative setting include antibiotics, latex, neuromuscular blockers, and chlorhexidine.^{9,10} Diagnostic criteria are based on physical examination findings shown in Figure 1. In cases involving an unknown allergen, numerous clinical manifestations are needed for diagnosis. This is especially important in cases of suspected anaphylaxis to sugammadex, in which bradycardia has been described, which could lead to hypotension through decreased cardiac output.¹¹ Serum tryptase levels can be drawn 15 minutes to 3 hours after suspected anaphylaxis to aid in the diagnosis retrospectively, but it is essential to recognize

that this laboratory investigation is not specific to anaphylaxis. Levels of tryptase may also be within normal limits during an anaphylactic reaction and do not rule in or rule out an anaphylactic reaction with certainty. Preferably, serial tryptase levels are drawn throughout the acute phase of an anaphylactic reaction and afterward, as this may yield more helpful information because a trend may be established instead of relying on a single value. First-line evidence-based therapy for anaphylaxis is epinephrine.⁸

Sugammadex is a modified cyclodextrin, approved for clinical use by the FDA in the United States in December 2010 for reversal of neuromuscular blockade of the aminosteroid neuromuscular blocking agents rocuronium and vecuronium. It was available much earlier in Europe (2008) and Japan (2008) and is currently licensed for use in over 70 countries. The delay in FDA approval was due to concerns regarding the high incidence of hypersensitivity reactions.¹

The drug’s package insert⁴ provided by Merck and Company, Incorporated (Whitehouse Station, NJ) states that the rate of anaphylaxis is 0.3%, but this was based on a single small study of 299 healthy volunteers who received injections of sugammadex, with 1 patient suffering from an anaphylactic reaction. The package insert also refers to a previous study of similar design with a rate of anaphylaxis of 1%; 3 of 298 healthy volunteers suffered from an anaphylactic reaction.

While several case studies have been reported in the literature, a recent single Japanese retrospective study determined the incidence of anaphylaxis at 0.039% (approximately 1 of 2500 administrations) based on a sample of 15,479 patients who received 23,608 total doses. This was performed at a single Japanese hospital and was based on reported cases of anaphylaxis voluntarily submitted to a critical incidents database.⁷ It is, therefore, possible that the incidence could have been even higher, as some of the anaphylactic reactions may not have been reported. In fact, the Japanese Society of Anesthesiologists (JSA) has issued warnings about sugammadex-induced anaphylaxis numerous times since March 2011 due to the high numbers of cases of anaphylaxis reported to the agency and pointed out that the rate of anaphylaxis was likely even higher than recognized.

The mechanism of action of anaphylaxis from sugammadex is unknown. Cyclodextrins are pervasive as food additives and in cosmetics, and one theory is that sensitization occurs by exposure to these products, thereby making previous exposure to sugammadex unnecessary to provoke an anaphylactic reaction. Supporting this notion is that many reported anaphylactic reactions to sugammadex occur in patients with no previous exposure to the drug, consistent with the 2 cases of anaphylaxis presented in this report. This could make the incidence of anaphylaxis to sugammadex variable by country or region due to variations in cyclodextrin exposure.¹² Such geographical differences due to suspected differential environmental exposure have been reported previously.¹³ Even studies investigating the overall rates of perioperative anaphylaxis have revealed conflicting results when those performed in different regions are compared, ranging from 1 in 18,600 to 1 in 353 anesthesia cases.¹² This underscores the need for jurisdiction-specific anaphylaxis rates that apply to the practitioners' patient population.

There are several limitations to this study. This was a single-center, retrospective study, and cases may have been inadvertently overlooked in the chart review process. Critical incidents are not reported into a critical events registry at our institution, and this could have served as another way to identify relevant cases and, therefore, could have possibly underestimated the incidence. Larger retrospective or prospective studies may be necessary to give a more accurate rate of anaphylaxis to sugammadex, given the rare nature of this event.

CONCLUSIONS

This is the first retrospective study to demonstrate that an incidence of anaphylaxis to sugammadex in a large-volume medical center in the United States is approximately 2 of 23,446 doses in 19,821 patients. The incidence is much lower than the only other previous retrospective single-center study in Japan,

which revealed an incidence of approximately 1 of 2500 administrations. This study, in comparison, combined 2 independent systematic search methods in the institutional EMR to optimize the accuracy of the search, with both identifying the same 2 patients. More extensive retrospective or prospective studies may be needed to estimate the incidence of rare anaphylactic reactions to sugammadex more precisely. ■

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DISCLOSURES

Name: Mark A. Burbridge, MD.

Contribution: This author performed the literature review, reviewed and evaluated all patient charts, analyzed all the data, and wrote and approved the final manuscript.

This manuscript was handled by: Ken B. Johnson, MD.

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