JPPT | Case Series

Allergic Reactions to Sugammadex: A Case Series and Review of the Literature

Rita Banoub, MD; Emmanuel Alalade, MD; Jason Bryant, MD; Peter Winch, MD; and Joseph D. Tobias, MD

Sugammadex is a novel agent for the reversal of neuromuscular blockade; it acts by encapsulating rocuronium or vecuronium, eliminating the active compound from the circulation, thereby providing rapid and complete recovery even with profound or complete neuromuscular blockade. Clinical advantages, including reduced incidence of residual blockade, decreased nausea and vomiting, decreased dry mouth, less change in heart rate, and reduced pulmonary complications, have been demonstrated when comparing sugammadex to conventional agents, such as neostigmine, that inhibit acetylcholinesterase. Although generally safe and effective, anaphylactoid and allergic reactions have been reported with sugammadex. The potential for hypersensitivity reactions with sugammadex and previous reports from the literature, as well as diagnostic and treatment strategies, are presented in 3 pediatric cases.

ABBREVIATIONS Ig, immunoglobulin; PACU, postanesthesia care unit

KEYWORDS allergy; anaphylactoid reaction; anaphylaxis; pediatric anesthesiology; sugammadex

J Pediatr Pharmacol Ther 2023;28(4):374–379

DOI: 10.5863/1551-6776-28.4.374

Introduction

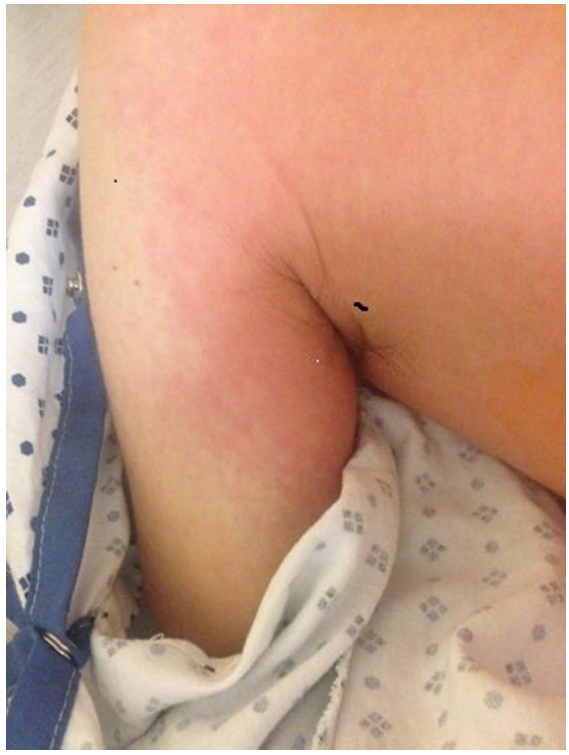
Sugammadex is a γ-cyclodextrin molecule with a hollow cone–like shape that acts by encapsulating aminosteroid neuromuscular blocking agents, such as rocuronium or vecuronium, thereby providing selective reversal of neuromuscular blockade.[1,2] Sugammadex provides more effective and complete reversal of neuromuscular blockade than neostigmine, with a lower adverse effect profile.[3,4] Despite its availability in Japan and Europe for more than a decade, it was not approved for clinical use in adults by the US Food and Drug Administration until December 2015. One of the reasons for its delayed release in the United States was concerns for hypersensitivity reactions. Although most of these hypersensitivity reactions result only in mild symptoms, such as nausea or rash, there is a small but definite risk of potentially life-threatening symptoms, such as airway edema, bronchospasm, and cardiovascular collapse.[2] We present 3 pediatric-age patients who developed hypersensitivity reactions to sugammadex at Nationwide Childrens Hospital from 2016 to 2020, identified by the anesthesia faculty and staff.

Case Reports

Patient 1. A 6-day-old, 3.5-kg, term infant presented for arterial switch repair for transposition of great arteries. The surgical procedure, including anesthetic care (rocuronium, fentanyl, and sevoflurane), and cardiopulmonary bypass were uneventful. During completion of the procedure with closure of the sternum, residual neuromuscular blockade was reversed with 4 mg/kg sugammadex. Two minutes later, severe bronchospasm was noted with difficulties with ventilation, increased peak inflating pressure to 33 cm H_2O, decreased end-tidal carbon dioxide to 6 mm Hg, and hypotension (blood pressure 29/20 mm Hg). The ensuing resuscitation included the administration of 2.8 mcg/kg phenylephrine followed by 2 epinephrine boluses of 1.4 and 2.8 mcg/kg, and the administration of 10 mL/kg isotonic crystalloid. The sternum was reopened to rule out cardiac tamponade and an epinephrine infusion started at 0.02 mcg/kg/min for continued hypotension. Over the ensuing 15 to 20 minutes, the hemodynamic and respiratory symptoms improved and the patient was transferred to the cardiothoracic intensive care unit. The following day, the epinephrine drip was discontinued and the sternum was closed. The patient's trachea was extubated on postoperative day 3. The remainder of his postoperative course was unremarkable.

Patient 2. A 2-month-old, 6-kg infant presented for resection of a nasal chondromesenchymal hamartoma. Following completion of the surgical procedure, residual neuromuscular blockade from rocouronium was reversed with 3.3 mg/kg sugammadex, followed in less than 5 minutes by an additional 1.7 mg/kg dose when signs of inadequate reversal were noted. The patient's trachea was successfully extubated and he was transported to the postanesthesia care unit (PACU) without incident. Within 30 minutes in the PACU, the patient

Image. Shoulder, chest, and upper arm of patient 3 showing the erythematous urticarial rash noted when the surgical drapes were removed. The rash resolved following the administration of intravenous diphenhydramine.



was noted to have a generalized rash, tachycardia (heart rate of 141 bpm), decreased oxygen saturation (80%), and diffuse wheezing. Treatment included the intravenous administration of 0.3 mcg/kg epinephrine and 0.8 mg/kg diphenhydramine, which resulted in improvement of his symptoms. Given the type of surgery, which mandated avoidance of positive pressure ventilation by mask, his trachea was reintubated after the administration of 3 mg/kg propofol and 16 mcg/kg atropine, and he was admitted to the pediatric intensive care unit. During the next 24 hours, he received dexmedetomidine for sedation. Other medications included acetaminophen and cefazolin. No further cardiovascular or respiratory symptoms were noted. His trachea was extubated on postoperative day 1 and the remainder of his postoperative course was uneventful.

Patient 3. A 14-year-old, 47.9-kg adolescent with a history of developmental delay and an intractable seizure disorder presented for emergency aspiration of an intra-abdominal cyst in the interventional radiology department. After an uneventful procedure, residual neuromuscular blockade from rocuronium was reversed with 2 mg/kg sugammadex. In the PACU, 10 minutes after sugammadex administration, a generalized skin rash (Image) was noted without any other systemic symptoms. The rash subsided following the administration of 1.2 mg/kg diphenhydramine.

Discussion

Perioperative allergic reactions are rare, but can be the cause of serious morbidity and mortality during anesthetic care.[5] The incidence of anaphylaxis to a specific substance in the perioperative period is difficult to accurately establish and has been the subject of debate.[6] The Boston Collaborative Drug Surveillance study reported an incidence of 1:900 to 1:20,000; the largest multicenter study in France reported an incidence of 1:6,000; and in 2018, the overall incidence of perioperative anaphylaxis in the 6th National Audit Project was estimated to be 1:10,000 in adults and 2.7:100,000 in infants and children.[7–9]

These reactions to medications are generally classified as an immune-related anaphylactic or non–immune-related anaphylactoid reaction.[10,11] Anaphylactic reactions are allergic reactions due to antigens cross-bridging immunoglobulin (Ig) E IgE or IgG antibodies attached to mast cells and basophils with the resultant release of inflammatory mediators, including histamine, kinin, slow reacting substance of anaphylaxis, eosinophilic chemotactic factor, platelet-activating factor, and prostaglandin. In contrast, non–immune-related anaphylactoid reactions are due to a direct, nonspecific activation of mast cell and basophil activation with the release of histamine and other inflammatory mediators. These latter reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions. The clinical manifestations of allergic reactions under anesthesia vary in intensity from mild hypersensitivity reactions manifested as cutaneous signs of erythema, urticaria, and edema, to severe anaphylactic shock with systemic manifestations, including cardiac arrest, hypotension, bronchospasm with alterations in capnography, increased peak inflating pressure, and oxygen desaturation.

Various investigators have outlined the most common agents causing allergic reactions during anesthetic care, with the incidence varying according to the years of the study. Mertes et al[12,13] identified latex, antibiotics, and neuromuscular blocking drugs as the most common perioperative anaphylaxis triggers in children in a study spanning 1997 to 2004. The adoption of a latex-free environment in most countries has eliminated sensitivity to latex and, subsequently, decreased anaphylaxis to this trigger during perioperative care. Current perioperative triggers most commonly include antibiotics, neuromuscular blocking agents, chlorhexidine, and dyes used for radiologic imaging.[7] However, the changing practice of anesthesia with the introduction and increased use of sugammadex may be changing the etiology of perioperative allergic reactions.

Data from the preclinical trials estimated the incidence of allergic phenomena to be approximately 0.3% in healthy volunteers, requiring treatment with only an H_1-antagonist, such as diphenhydramine. Anecdotal reports have detailed clinical symptoms spanning the entire spectrum of allergic reactions, including a mild skin rash, urticaria, bronchospasm, and/or anaphylactic shock requiring resuscitation.[14–18] Additional reports have demonstrated the potential for the complex of sugammadex with rocuronium to evoke allergic reactions.[19–21] In a comprehensive review of the published literature, which included patients of all ages, Tsur and Kalansky[22] identified 15 cases of hypersensitivity reactions following the administration of sugammadex. Fourteen of the reactions occurred within 5 minutes of administration. A total of 11 of 15 met the World Anaphylaxis Organization criteria for anaphylaxis. Of the 11 patients who underwent confirmatory skin testing, 10 had a positive result. The authors cautioned that awareness should be raised for drug-induced hypersensitivity reactions during the critical 5-minute period immediately following sugammadex administration. Subsequently, a single-center, retrospective review identified 6 cases of possible anaphylaxis to sugammadex during a 3-year period including 15,479 patients who received sugammadex.[23] During the study period, the total number of surgical cases was 23,608, the overall incidence of intraoperative hypersensitivity reactions was 0.22%, and the incidence of anaphylaxis was 0.059%. The incidence of anaphylaxis associated with sugammadex was 0.039%, which led the authors to conclude that the incidence of sugammadex-associated anaphylaxis could be as high as that of any other medication administered intraoperatively, including the neuromuscular block agents succinylcholine or rocuronium. However, other investigators have suggested a lower incidence, perhaps no greater than that of placebo or neostigmine.[24–26] Although the mechanism of action of anaphylaxis from sugammadex is unknown, exposure to cyclodextrins in food additives and cosmetics may contribute to allergic reactions to sugammadex following its first administration.[27]

In our 3 patients, signs and symptoms suggestive of an allergic reaction occurred after the administration of sugammadex. The onset was somewhat prolonged in 1 patient, occurring approximately 30 minutes after administration. However, no other medications had been administered during this time period that could have accounted for the signs and symptoms that were seen. Signs and symptoms included hemodynamic and respiratory involvement in our first patient, cutaneous and respiratory involvement in the second, and only cutaneous involvement in the final patient. Two patients required the administration of epinephrine but the third received only the H_1-antagonist diphenhydramine. A tryptase serum concentration was obtained in 2 of our patients (patients 1 and 2; see Table), and although it was not elevated, the timing of the blood draw was delayed. Additional laboratory or clinical investigation was not performed.

The diagnosis of an allergic reaction during anesthesia should include a detailed history of previous and current medications. Potential biologic investigations include mediator release assays for histamine and tryptase at the time of the reaction, specific IgE assays, skin tests, and basophil activation assays.[12] Mediator release assays measure histamine and tryptase concentrations in the patient's serum.[28,29] These mediators are released after mast cell and basophil activation and degranulation due to the allergic reaction. However, these are non-specific determinants, only demonstrating that mast cell degranulation occurred, not identifying the specific agent. Histamine concentrations are highest immediately at the start of the allergic reaction and should be measured in the first hour. In contrast, tryptase reaches a peak concentration at 30 to 60 minutes and has a half-life of 90 minutes. Specific IgE assays may be available to detect IgE antibodies directed against a specific medication. These tests can be performed at the time of the reaction or several weeks later. Skin testing remains the diagnostic test of choice for an IgE-mediated reaction. Intradermal skin or prick tests are performed 4 to 6 weeks after a reaction. When considering sugammadex, skin testing with both sugammadex and the sugammadex-rocuronium complex should be considered. Without standardized skin testing there is questionable value, especially with respect to a negative test, which may have no predictive power. Different concentrations for skin testing have been used. A relatively low concentration of 1:1000 or 1:100 is recommended because it maintains sensitivity while decreasing the possibility of irritation or reactions from a more concentrated solution. Diagnostic testing for sugammadex-induced anaphylaxis is still somewhat limited because sugammadex-specific IgE antibodies and skin testing are still in development and may not be universally available. Given the expertise involved in this area, consultation with a pediatric allergist is recommended for skin testing. Regardless of the agent involved, the management of allergic reactions varies according to severity. Delayed diagnosis and the late administration of epinephrine may lead to a prolonged or biphasic clinical course, or even a fatal outcome.[30] Treatment of severe allergic reactions include the early administration of vasoactive agents, most importantly epinephrine, intravenous fluids, bronchodilators, corticosteroids, and antihistamine.[31]

In summary, we report 3 pediatric-age patients who developed hypersensitivity reactions to sugammadex after receiving a dose ranging from 2 to 5 mg/kg. Using the adverse drug reaction probability scale, all 3 cases were within the probable range.[32] In most of the cases reported in the literature, the onset time of symptoms has been less than 5 minutes (median, 3).[33] The most

Table. Patient Demographics and Clinical Information

Patient	Demographic Data	ASA Class	Allergies	Home and Hospital Medications	Intraoperative Medications	Time to Symptoms (min)	Treatment	Testing
1	6-yr-old, 3.48-kg female	4	None	Alprostadil, fentanyl, total parenteral nutrition	Dexmedetomidine, milrinone, fentanyl, rocuronium, cefazolin, tranexamic acid, dexamethasone, phenylephrine, acetaminophen, magnesium, protamine, calcium chloride	2	Epinephrine (bolus and infusion), sodium bicarbonate, albuterol, fluid bolus	Tryptase ≤2 μ/L†
2	2-mo-old, 6.05-kg male	1	None	Cholecalciferol	Albumin (5%), cefazolin, rocuronium, dexamethasone, fentanyl, calcium gluconate, Dexmedetomidine, acetaminophen, packed red blood cells	30	Epinephrine bolus, diphenhydramine	Tryptase ≤2 μ/L†
3	14-yr-old, 47.9-kg male	3	None	Lamotrigine, oxcarbazepine, lacosamide, omeprazole	Fentanyl, propofol, lidocaine, dexamethasone, ondansetron, rocuronium	10	Diphenhydramine	None

ASA, American Society of Anesthesiologists' physical classification

* Reference lab value for normal serum tryptase level is less than 10.9 μg/mL.
† Tryptase levels were drawn 2 hours 37 minutes and 4 hours 1 minute after the administration of sugammadex.

common signs and symptoms included hypotension, tachycardia, erythema, and oxygen desaturation. Rapid diagnosis with the early recognition of signs and symptoms of anaphylaxis followed by immediate treatment including the administration of epinephrine are essential to allow for prompt treatment and a successful outcome.[30]

Article Information

Affiliations. Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital and The Ohio State University, Columbus, OH.

Correspondence. Rita Banoub MD; rita.banoub@nationwidechildrens.org

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. Review of these cases and presentation in this format was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). Written consent was not required.

Submitted. December 10, 2020

Accepted. March 12, 2021

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