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Title: The role of sugammadex in the treatment of anaphylaxis due to rocuronium in children: extrapolation from adult and animal reports

Running title: Rocuronium anaphylaxis

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Abstract

In general, allergic reactions are generalized hypersensitivity processes triggered by different antigenic stimuli resulting in the end effect of mast cell degranulation and adverse physiologic effects. During the perioperative period, the most commonly identified agents include antibiotics, neuromuscular blocking agents (rocuronium and succinylcholine), chlorhexidine, and iodinated dyes for radiologic imaging. Sugammadex is a novel agent for the reversal of neuromuscular blockade achieved with rocuronium or vecuronium. Its unique mechanism of action whereby it encapsulates and forms a one-to-one complex with rocuronium has led to its anecdotal use as an adjunct in the treatment of anaphylactic and anaphylactoid reactions following rocuronium. The current manuscript discusses the potential use of sugammadex in the treatment of allergic reactions following the administration of rocuronium, reviews previous anecdotal reports of its use in these scenarios, and provides recommendations for future care.

Key words: anaphylaxis, anaphylactoid reactions, intraoperative care, rocuronium, sugammadex

Introduction

Anaphylaxis and anaphylactoid reactions are generalized hypersensitivity processes triggered by different antigenic stimuli resulting in the end effect of mast cell degranulation and adverse physiologic effects. They remain an uncommon yet potentially life-threatening event during intraoperative anesthetic care.¹ Anaphylactic reactions are allergic reactions due to antigens cross bridging 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 result from the direct, nonspecific activation of mast cells and basophils with the release of histamine and other inflammatory mediators. During general anesthesia, the clinical manifestations may be difficult to separate from other etiologies due to the concomitant administration of various pharmacologic agents and the impact of anesthetic care and the surgical procedure. Common clinical findings include 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.

The incidence of anaphylaxis to a specific substance in the perioperative period is difficult to accurately establish and has been the subject of debate.¹ 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.²⁻⁴ Rapid

diagnosis with emergent treatment should be the goal in the management of anaphylactic reactions as delayed diagnosis and delayed administration of effective therapy including epinephrine may result in increased morbidity and mortality.⁵ The treatment algorithm also includes identifying and eliminating the causative antigen to prevent ongoing amplification of the process.

When attempting to identify the most common agents causing allergic reactions during anesthetic care, the incidence and inciting agents have varied according to the years of the study. Latex, antibiotics, and neuromuscular blocking drugs were previously identified as the most common perioperative anaphylaxis triggers in children.⁶ The adoption of a latex-free environment in most countries has eliminated sensitivity to latex and subsequently decreased anaphylaxis to this agent. A review using the Wake-Up Safe database recently identified antibiotics, neuromuscular blocking agents, chlorhexidine, and dyes used for radiologic imaging as the most common agents responsible for allergic reactions in pediatric-aged patients.⁷ Of the neuromuscular blocking agents, rocuronium and succinylcholine are most common.

Sugammadex (Bridion[®], Merck & Co, Whitehouse Stations, New Jersey) is a novel pharmacologic agent which received approval for clinical use from the United States Food & Drug Administration (FDA) in December 2015.⁸ Its unique mechanism of action differs completely from acetylcholinesterase inhibitors as it encapsulates rocuronium or vecuronium, providing rapid and complete recovery of neuromuscular blockade even in the presence of profound or complete block. Its novel chemical structure encapsulates and forms a one-to-one complex with rocuronium thereby eliminating it from circulation and reducing its effective concentration at the

neuromuscular junction. Its unique mechanism of action has led to its anecdotal use as an adjunct in the treatment of anaphylactic and anaphylactoid reactions following the administration of rocuronium. The concept behind its use makes sense on a molecular level as encapsulation of the offending molecule (rocuronium) and its removal from the effective circulation may halt further progression of the chemical process inciting the reaction.

A systematic search of PubMed® was conducted using the search terms sugammadex, rocuronium, allergic reactions, children, pediatric anesthesiology, and anaphylactoid reactions (November 2021). The abstracts from the publications were reviewed and those pertaining to the use of sugammadex to reverse allergic reactions to rocuronium were included for further review. The reference list of these publications was reviewed to ensure that all reports had been identified. The current manuscript discusses the potential use of sugammadex in the treatment of allergic reactions following the administration of rocuronium, reviews previous anecdotal reports of its use in these scenarios, and provides recommendations for future care.

Literature Review

Anecdotal clinical reports

The literature on this subject includes case reports involving a single patient, case series of 2-3 patients where sugammadex was successful, a few case reports where sugammadex was not successful, and a larger retrospective study involving cases reported to the Western Australia Anaesthetic Drug Reaction clinic (see below). The various anecdotal reports, the first of which was published in 2011, outlining the potential

successful use of sugammadex in ameliorating or reversing the clinical signs and symptoms following an allergic reaction to rocuronium, are summarized in table 1.⁹⁻²⁴ These reports include a total of 21 adult patients in whom sugammadex was administered following a suspected allergic reaction to rocuronium. Sixteen of the reports include a single case while one report includes two patients, and one includes 3 patients. The patients span a varied age range from 18 to 75 years of age. Of note, there was a preponderance of women with only two males and a total of 19 women in the total reported cohort of 22 patients. The patients had a variety of comorbid conditions with ASA physical status varying from II to IV. Onset of symptoms were generally rapid, immediately following the induction of anesthesia and the administration of rocuronium. Clinical signs and symptoms varied including some combination of hemodynamic instability (hypotension), respiratory compromise (increased airway pressure, difficult ventilation, decreased end-tidal carbon dioxide, and hypoxemia), and cutaneous rashes or erythema. In several cases, the hemodynamic instability was severe enough to require cardiopulmonary resuscitation. In all of the patients, resuscitation efforts were failing with ongoing hemodynamic instability despite the administration of isotonic fluids and vasoactive agents including epinephrine in the majority of patients or clinically significant respiratory compromise (oxygen desaturation, bronchospasm, or elevated airway pressures). There was generally limited response to pharmacologic therapy with vasoactive agents including epinephrine in the majority of patients, corticosteroids, and antihistamines. The allergic reaction was attributed to rocuronium although many of the patients also received propofol and opioids (remifentanyl, fentanyl, sufentanyl, morphine). Postoperative support for the diagnosis of an allergic reaction to rocuronium was not

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obtained in all patients, but in several included an elevated serum tryptase or histamine level, immunoassays identifying IGE antibody to rocuronium or basophil activation in response to rocuronium or positive intradermal skin testing. One interesting report noted positive skin testing to rocuronium, negative to sugammadex, and negative to the rocuronium-sugammadex complex.²¹

Both the dose of sugammadex and the timing of its administration varied significantly among the patients. The majority of the reports administered sugammadex doses of 4-6 mg/kg while some authors reported a larger dose (10-14 mg/kg), close to the dose of 16 mg/kg which is recommended for reversal of deep or complete neuromuscular blockade such as occurs immediately after an intubating dose of rocuronium (0.6-1.2 mg/kg). There was also variability in the timing of sugammadex administration and the recognition of anaphylaxis, the onset of clinical symptoms, and the administration of rocuronium. In some reports, sugammadex was administered early (within 10 minutes of rocuronium) whereas in others, it was administered at a medium timeframe (20-30 minutes) or even late at 50-80 minutes. Reversal of clinical signs and symptoms of the allergic reaction was generally rapid.

Despite the large number of anecdotal reports outlining the successful use of sugammadex to reverse allergic reactions to rocuronium, the reported literature has not been uniformly positive.²⁵⁻²⁷ Raft et al. reported their experience and noted what they called “slow recovery after sugammadex bolus after rocuronium-induced anaphylaxis”.²⁵ After the induction of anesthesia with midazolam, sufentanil, propofol, and ketamine followed by NMB with rocuronium (0.7 mg/kg), hypotension, bronchospasm, oxygen desaturation, and increased airway pressures were noted. When there was limited

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response to multiple doses of epinephrine and isotonic fluid, sugammadex (14 mg/kg) was administered 13 minutes after the onset of anaphylaxis. Additional epinephrine as well as isotonic crystalloids and colloids were administered. There was clinical improvement after two more bolus doses of epinephrine. Postoperatively, they noted an elevated serum tryptase and a positive skin test positive for rocuronium. The authors commented that to the best of their knowledge, their case was the first failure of a response to sugammadex in a patient with a confirmed allergic reaction to rocuronium.

Marcharadze et al. reported their experience with the administration of sugammadex to treat a rocuronium-induced allergic reaction in a 66-year-old man presenting for aortic valve replacement and coronary artery bypass.²⁶ This report is discussed separately as the response to sugammadex was unclear and at best, this should likely be considered a delayed response based on the sequence of events reported by the authors. Anesthesia was induced with midazolam, propofol, and fentanyl. NMB was provided by rocuronium (100 mg). Immediately after the administration of rocuronium, there was hypotension (40/10 mmHg) and poor respiratory compliance requiring CPR. There was no response to bolus doses of metaraminol, epinephrine, isotonic fluid resuscitation, and the administration of packed red blood cells. Sugammadex (16 mg/kg) and 30 mL of 20% intralipid were administered. There was transient and mild improvement in the heart rate, but the patient was still hypotensive with blood pressure of 60/40 mm Hg. As preparations were being made for ECMO, 32 minutes after the initiation of resuscitation, the BP stabilized at 100/50 mmHg. The patient was supported with infusions of epinephrine, norepinephrine, and vasopressin. The patient was

discharged home with no sequelae. Skin prick and intradermal testing were positive for rocuronium sensitivity.

The largest study to date included review of a total of 13 patients from Western Australia.²⁷ The study was published from data collected by the Western Australian Anaesthetic Drug Reaction Clinic (WAADRC), a specialized diagnostic center for the investigation of perioperative allergic reactions. Between October 2010 and October 2014, the authors reviewed all cases of presumed rocuronium-induced anaphylaxis. Of the 13 such cases, only 8 were definitely proven to be allergic reactions (type 1 hypersensitivity) to rocuronium based on postoperative laboratory testing. Three were triggered by an antibiotic and two were non-immunologically mediated. Response to treatment was scored by the treating anesthesiologist and evaluated based on the hemodynamic response. Clinical improvement was seen in 6 of the 13 cases after the administration of sugammadex, three of which were associated with a non-rocuronium trigger. Of the three cases in which the treating anesthesiologist thought that sugammadex was beneficial, one case was not caused by rocuronium, one patient had no improvement in blood pressure after sugammadex, and one patient required 8.5 times as much epinephrine after as compared to before sugammadex. These findings led the authors to suggest that sugammadex was not helpful in mitigating the clinical consequences of rocuronium-induced anaphylaxis.

Animal data

Various animal studies have attempted to define the effect of sugammadex on the inflammatory and immunologic reactions in rocuronium-induced allergic reactions.

Using biochemical, light microscopy, and immunohistochemical parameters, Yesilintas et al. investigated the impact of sugammadex on changes caused by rocuronium in the lungs of Sprague-Dawley rats.²⁸ The rats were evenly divided into 4 study cohorts with the control group (C) receiving saline, group 2 receiving rocuronium (R), group 3 receiving sugammadex (S), and group 4 receiving both rocuronium and sugammadex (RS). Various chemical and histopathologic indications of inflammation including immunoglobulin E, C-reactive protein (CRP), peri-bronchial and alveolar septal lymphocytic infiltration, thickening of the alveolar membranes, total mast cells, and tryptase-positive mast cells were significantly lower in Group RS than that of Group R. The authors concluded that these findings supported the clinical reports of improvement in clinical status following the administration of sugammadex in patients with suspected allergic reactions to rocuronium.

A subsequent animal investigation investigated mast cell numbers and degranulation in rat portal triads following the administration of rocuronium, sugammadex (15 mg/kg), sugammadex (100 mg/kg), and rocuronium with sugammadex.²⁹ Total mast cell numbers and tryptase positive mast cells were significantly higher in the rocuronium only group compared to other groups. The authors suggested that sugammadex may be beneficial in rocuronium-induced anaphylaxis.

In vitro and intradermal in vivo testing

Pre-incubation with sugammadex demonstrated a dose dependent inhibition of rocuronium-induced cell activation in an in vitro model using flow cytometric analysis of

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basophils from rocuronium-allergic patients.³⁰ However, in a second in vitro experiment, when the basophils were first activated with rocuronium followed by the administration of sugammadex, activation could not be blocked completely even with high concentrations of sugammadex. This led the authors to conclude that although encapsulating rocuronium with sugammadex can prevent in vitro basophil activation, it cannot stop the process once activated. Therefore, it is unlikely that administration of sugammadex will mitigate rocuronium-induced anaphylaxis.

A follow-up study from the authors of the WAADRC study used intradermal skin testing on 10 patients who had previously suffered from a life-threatening episode of rocuronium-induced anaphylaxis.³¹ All patients reacted normally with positive histamine and negative saline control tests. None reacted to intradermal sugammadex. Although pre-mixed sugammadex and rocuronium significantly attenuated the cutaneous response, the administration of sugammadex through a fixed intradermal needle after the administration of rocuronium did not attenuate the reaction. The area under the curve for rocuronium followed by sugammadex was not less than rocuronium alone. The authors concluded that sugammadex conceals the allergenic epitope of the rocuronium molecule but does not modify cell degranulation once it has been activated and therefore is unlikely to modify the clinical course of an allergic reaction to rocuronium once it has been initiated.

Discussion

The anecdotal literature outlines the potential utility of sugammadex in the treatment of adult patients with allergic reactions related to the administration of

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rocuronium. To date, there are no reports of its use for this clinical indication in pediatric-aged patients as the youngest reported patients are 18 and 19 years of age. However, given the potential for morbidity and mortality related to allergic reactions to medications including rocuronium in children, consideration of this novel treatment approach may be applicable in children and adolescents.

Before the theory was put to a clinical test, Jones and Turkstra postulated the potential for sugammadex to prevent propagation of rocuronium-induced anaphylaxis as early as 2010.³² They suggested that sugammadex may effectively remove free rocuronium molecules from the circulation thereby slowing down or halting the immunologic process responsible for anaphylaxis. However, they further cautioned that sugammadex may not be effective as the antigenic portion of the rocuronium molecule containing the ammonium group protrudes from the sugammadex molecule. A similar concern has been expressed by other investigators.³³ As a major factor in the management of anaphylaxis is removal of the triggering agent to mitigate the cascade reaction, it is appropriate to assume that the timing of the administration of sugammadex (i.e., how quickly it is administered after the inciting event, rocuronium) may impact the outcome. Given the retrospective nature of the case reports, it was not possible to determine an exact estimate as to how quickly sugammadex must be administered to achieve its maximum efficacy and a time after which its use will be ineffective. Many reports noted early administration (within 10 minutes of the onset of signs and symptoms), some did not note the timing, while two reported what appeared to be a clinical response even when sugammadex was administered 60 or 80 minutes after resuscitation was initiated.

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The theoretical suggestion regarding the utility of sugammadex for rocuronium-induced allergic reactions was followed by the first anecdotal report of its use by McDonnell et al in 2011.⁹ This initial report was followed by several other anecdotal reports suggesting the successful use of sugammadex in patients with rocuronium-induced allergic reactions. The obvious implications of and relative limitations of single case reports must be recognized as there are no prospective controlled data to support the use of sugammadex in this clinical scenario

Despite these anecdotal successes, the report of Platt et al from the WAADRC has raised significant concerns and questioned the utility of sugammadex in reversing rocuronium-induced allergic reactions.²⁷ The authors point out key factors in their review of 13 cases of what was thought to be rocuronium-induced anaphylaxis including that there was hemodynamic improvement after sugammadex administration in cases that were not triggered by rocuronium, not all cases that were caused by rocuronium had a treatment response to sugammadex, the case records did not always support the treating anesthesiologist's impression of efficacy, and the severity of the anaphylactic response, the mast cell tryptase level and the epinephrine dosing varied significantly among the cases of rocuronium-triggered anaphylaxis.²⁷ Platt et al. also offered non-immunologic mechanism which may explain the potential utility of sugammadex in patients experiencing hemodynamic compromise, regardless of its cause. With reversal of neuromuscular blockade, sugammadex may increase skeletal muscle tone and hence compression of intra-abdominal and intramuscular vessels thereby reducing venous capacitance result in an increase in venous return, preload, and cardiac output. Minimizing the depth of anesthesia along with reversal of neuromuscular blockade may

improve hemodynamic performance through various mechanisms, albeit at the risk of patient movement during a critical clinical scenario.

Summary

Despite the potential utility of sugammadex in this clinical scenario, its use should be considered carefully, and the risk-benefit ratio determined. Sugammadex itself can cause allergic reactions, the incidence of which is only now being recognized and investigated.^{34,35} Sugammadex binds amino-steroid molecules and there is the potential for sugammadex to bind other steroid molecules including hydrocortisone which may have undesirable physiologic effects, especially in the setting of an allergic reaction. The first priority in the treatment of any suspected anaphylactic reaction is the implementation of well-established therapies. The latter is of significant importance as a delay in diagnosis or the late administration of epinephrine may lead to a prolonged or even fatal outcome. Treatment of an intraoperative allergic reaction includes adherence to standardized resuscitation pathways with the administration of vasoactive agents most importantly epinephrine, intravenous fluids, bronchodilators, corticosteroids, and antihistamines.^{5,6,36,37} A systematic approach is necessary for the diagnosis of an intraoperative allergic reaction, confirmation of the offending agent, its management under anesthesia, and the process for appropriate postoperative laboratory and skin testing to guide future anesthetic care.³⁸ The administration of sugammadex should not precede or preclude these other therapies and diagnostic investigations. If ongoing neuromuscular blockade is needed, non-aminosteroid agents (cis-atracurium, atracurium or succinylcholine) should be used.

Because of the lower reporting rate of negative outcomes and an unclear mechanism as to how sugammadex may mitigate rocuronium anaphylaxis, it is too early to conclude that sugammadex will always be useful in this clinical scenario. Pending further investigations, consideration should be given to the administration of sugammadex as adjunctive therapy to a patient with rocuronium-induced anaphylaxis if traditional treatment is failing and there is a high index of suspicion of rocuronium being the causative agent. The use of sugammadex in rocuronium-induced allergic reactions remains off-label. There remains no firm evidence-based medicine to prove its efficacy or to provide clinical guidance for dosing. Based on a theoretical construct which suggests the benefit of removing all rocuronium from the circulation, it would appear appropriate to use the dose (16 mg/kg) required for reversal of deep neuromuscular blockade.

Reflective Questions

1. What is the physiologic rationale behind the use of sugammadex for the treatment of patients with allergic reactions following the administration of rocuronium?
2. What does the evidence-based literature say regarding the efficacy of sugammadex in treating allergic reactions to rocuronium?
3. Where in the treatment algorithm of allergic reactions to rocuronium should sugammadex be placed?
4. What are the potential concerns with administering sugammadex to a patient with an allergic reaction to rocuronium?

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Table 1: Reports of sugammadex to reverse allergic reactions to rocuronium

<i>Author and reference</i>	<i>Demographic data</i>	<i>Clinical signs and symptoms of allergic reaction and initial treatment</i>	<i>Dose and timing of sugammadex (how long after rocuronium)</i>	<i>Outcome</i>
McDonnell NJ et al. ⁹	33-year-old, 77 kilogram woman for laparoscopy.	Induction with propofol and fentanyl. NMB with rocuronium (0.4 mg/kg). Thirty seconds later, difficult bag-valve-mask ventilation. No palpable carotid pulse. Standard ACLS protocol including epinephrine with no ROSC.	Sugammadex (6.5 mg/kg) administered 19 minutes after start of event. Forty-five seconds later, the patient reached for the ETT. Sedated and treated with corticosteroids.	Tracheal extubation 30 minutes after ICU arrival. Uneventful recovery. Elevated serum tryptase and positive skin testing for rocuronium.
Funnell AE et al. ¹⁰	44-year-old, 78 kilogram woman for laparoscopic cholecystectomy	Induction with propofol and fentanyl. NMB with rocuronium (50 mg). Difficult bag-valve-mask ventilation, loss of pulse oximetry plethysmograph, hypotension, tachycardia, erythema. Treated with epinephrine, isotonic fluid, hydrocortisone, and antihistamine	Sugammadex (400 mg) administered one hour after onset of symptoms. Within 2.5 minutes, hemodynamic and respiratory status improved.	Epinephrine infusion decreased and then discontinued. Trachea extubated shortly afterwards. Elevated tryptase level and positive skin test.
Kawano T et al. ¹¹	62-year-old, 45 kilogram woman for modified radical mastectomy.	Induction and maintenance with remifentanyl and propofol. NMB initially with vecuronium followed by rocuronium. Immediately after rocuronium, hypotension and generalized urticarial rash. Treated with ephedrine, isotonic fluid, and Trendelenburg position with minimal improvement.	Due to no improvement in blood pressure and continued spread of rash, sugammadex (200 mg) administered after 30 minutes. Rash resolved and BP improved. Proceeded with surgery.	Remainder of perioperative course unremarkable. Refused allergy evaluation.
Barthel F. et al. ¹²	44-year-old, morbidly obese woman with chronic renal failure, hypertension, and later allergy for incisional hernia repair.	Induction with propofol and sufentanil. NMB with rocuronium (80 mg). Intubated after 2 minutes. Immediate hypotension and increased airway pressure. Bolus of epinephrine and isotonic fluid. Temporary improvement of hemodynamic status, but then multiple doses of epinephrine and methylprednisolone.	Sugammadex (12 mg/kg) after initial bolus dose of epinephrine and fluid. Transient improvement. Additional sugammadex (400 mg) when hypotension/rash reappeared and additional bolus doses of epinephrine/epinephrine infusion did not help. Hemodynamic status improved	Weaned off epinephrine infusion over next 10 hours. Allergy testing (serum immunoassay) identified rocuronium as allergen.
Badaoui R et al. ¹³	52-year-old, 77 kilogram woman for laparoscopic resection of a rectal tumor.	Induction with propofol and sufentanil. NMB with rocuronium. Two minutes later, hypotension, erythema, and oxygen desaturation. Isotonic fluid and epinephrine boluses (total of 6 mg) followed by infusion.	Sugammadex (1000 mg) administered 20 minutes after start of resuscitation. Five minutes later, return of carotid/radial pulses with restoration of hemodynamic function and resolution of erythema.	Weaned off vasopressors after one hour, discharged home after 48 hours. Elevated serum histamine, tryptase, and rocuronium-specific IgE. Positive skin test for rocuronium

Barbosa FT et al. ¹⁴	62-year-old 72 kilogram woman for epidural hematoma drainage	Induction with propofol and fentanyl. NMB with rocuronium. Immediately after intubation, hypotension, tachycardia, rash, and oxygen desaturation. Treated with epinephrine and isotonic fluid.	Five minutes after rocuronium, sugammadex (700 mg) administered. Additional single 0.3 mg of epinephrine and fluid. Two minutes later, stable hemodynamic status and resolution of other clinical symptoms.	Extubated after completion of surgery. No postoperative concerns.
Motamed et al. ¹⁵	61-year-old 45 kilogram woman for osteoplasty.	Premedicated with propranolol, hydroxyzine. Induction with propofol, remifentanyl. NMB with rocuronium (0.6 mg/kg). Hypotension, tachycardia, rash, high airway pressure, low end-tidal CO ₂ , wheezing. Treated with ephedrine, lowering inhaled agent, and epinephrine (0.2 mg).	Fourteen minutes after tracheal intubation, sugammadex (4 mg/kg) administered. Increased blood pressure, decreased airway pressure, improved end-tidal CO ₂ .	Extubated and transferred to ICU. Stable hemodynamic status. Elevated histamine, tryptase, and anti-rocuronium IgE.
Ishikawa T et al. (article in Japanese) ¹⁶	19-year-old man for endoscopic sinus surgery.	Induction with propofol, fentanyl and sevoflurane. NMB with rocuronium. Tachycardia, cutaneous erythema, difficult to ventilate, carotid pulse not palpable. Treated with epinephrine.	Sugammadex administered. Restoration of hemodynamic function and resolution of cutaneous erythema.	Elevated tryptase level.
Conte B et al. ¹⁷	22-year-old 87 kilogram woman for laparoscopic cholecystectomy.	Induction with sufentanil, ketamine, and propofol. NMB with rocuronium (0.6 mg/kg). Two minutes later, skin rash, and non-recordable blood pressure. Treated with colloid, epinephrine boluses (total 700 µg). No improvement. End-tidal CO ₂ 1 mmHg	Sugammadex 1200 mg (13.8 mg/kg) administered 6 minutes after the onset of symptoms. One minute later, recovery of hemodynamic status and resolution of rash.	No postoperative problems. Elevated tryptase and histamine. Skin test positive for rocuronium.
Sirieux et al. ¹⁸	60-year-old, 92 kilogram woman for endoscopic pancreatic ultrasound.	Induction with propofol, ketamine and sufentanil. NMB with rocuronium (50 mg). Hypotension and oxygen desaturation 7 minutes after rocuronium. Unrecordable blood pressure within next few minutes. Treated with crystalloids and ephedrine. Diagnosed as grade III anaphylactic shock. Treated with bolus of epinephrine and epinephrine infusion started.	Sugammadex 400 mg (4.3 mg/kg) 10 minutes after rocuronium along with epinephrine. Systolic blood pressure 60-70 mmHg. Additional sugammadex (200 mg) 20 minutes after initial dose. Improved oxygen saturation and blood pressure 5 minutes of second dose of sugammadex.	Tracheal extubation. Epinephrine infusion discontinued 9 hours after the incident. Discharged after 48 hours. Elevated tryptase and histamine. Skin prick test positive for rocuronium.
Spoerl D et al. ¹⁹	36-year-old woman for abdominal surgery.	Induction with fentanyl, lidocaine, and propofol. NMB with succinylcholine and rocuronium. Antibiotic administered. At the end of procedure, generalized urticarial rash, bronchoconstriction, hypoxemia. No response to antihistamine, methylprednisolone, and nebulized epinephrine.	Sugammadex (400 mg) administered when other interventions failed. Rapid improvement in the symptoms	Intradermal skin testing positive for rocuronium.

Spoerl D et al. ¹⁹	48-year-old woman for resection of intracranial mass.	Induction with propofol and fentanyl. NMB with rocuronium (40 mg). Within a few minutes, profound hypotension and generalized urticaria developed. No improvement with hydrocortisone, an antihistamine, epinephrine, and isotonic fluids	Sugammadex (200 mg) administered 53 minutes after the induction of anesthesia. Rapid improvement in hemodynamic status.	Elevated tryptase level. Intradermal skin testing positive for rocuronium.
Spoerl D et al. ¹⁹	69-year-old woman for resection of a glioblastoma multiforme.	Induction with propofol, sufentanil, and ketamine. NMB with rocuronium. Severe hypotension developed within a few minutes. Unresponsive to isotonic fluids, epinephrine (total of 1.5 mg). Despite this, received a second dose of rocuronium (20 mg), 60 minutes after first dose.	Sugammadex (400 mg) administered 40 minutes after second dose of rocuronium. Blood pressure stabilized. Second dose of sugammadex (200 mg) was administered.	Tracheal extubation 20 minutes after second dose of sugammadex. Stable postoperative course. Normal tryptase level. Intradermal skin testing weakly positive for rocuronium.
De La Cruz I et al. ²⁰	36-year-old, 66 kilogram woman for laparotomy following blunt trauma abdomen.	Induction with midazolam, fentanyl, and propofol. NMB with rocuronium (1.2 mg/kg). Difficult bag-valve-mask and mechanical ventilation with oxygen desaturation. Minimal response to corticosteroids and inhaled β -agonist beta agonist.	Sugammadex (5 mg/kg) administered after some improvement of symptoms with corticosteroids and β -adrenergic agonist. Improvement in ventilation and resolution of symptoms noted in 2 minutes.	Stable postoperative course. Normal serum tryptase, IgE, and complement level. Skin test for rocuronium was positive. Basophil Activation test BAT positive for rocuronium.
Hashimoto M et al. ²¹	38-year-old, 48 kilogram woman for temporomandibular joint contrast radiography and tumor removal.	Induction with fentanyl and propofol. NMB with rocuronium (30 mg). Failed attempt at fiberoptic nasal endotracheal intubation. Hypotension and skin rash 2 minutes after rocuronium and 10 minutes after contrast administration. No response to methylprednisolone.	Sugammadex (4 mg/kg) administered. Rapid resolution of cutaneous symptoms and hypotension.	Stable postoperative course. Allergy test failed to identify responsible agent.
Hashimoto M et al. ²¹	18-year-old, 53 kilogram woman for mandibular surgery.	Induction with fentanyl, remifentanyl and propofol. NMB with rocuronium (40 mg). Cutaneous and hypotension with heart rate of 100. Treated with isotonic fluids and ephedrine.	Sugammadex (200 mg) administered. Improved hemodynamic status and reduction of skin rash.	Stable postoperative course. Refused allergy evaluation.
Binczak M et al. ²²	74-year-old 54 kilogram woman for airway endoscopy.	Induction with propofol and remifentanyl; NMB with rocuronium 25mg (0.46 mg/kg). Three minutes later, moderate hypotension, tachycardia increased airway pressure. Increased anesthetic depth, albuterol puffs. Two doses of 10 mcg epinephrine. Transient improvement.	Sugammadex 800 mg (15 mg/kg) administered (time after rocuronium not noted). Heart rate decreased in 5 min. No improvement in airway pressure. Third epinephrine (10 μ g) dose resulted in a decrease in airway pressure.	Extubated 5 minutes later. Elevated histamine level, normal tryptase level, positive serum-specific IgE. Skin test positive to rocuronium, negative to sugammadex and negative to mixture of rocuronium with sugammadex.

Takise Y et al. ²³	71-year-old, 70 kilogram man with coronary artery disease scheduled for tracheostomy due to need of prolonged mechanical ventilation.	Induction with sevoflurane. NMB with rocuronium (50 mg). Sudden hypotension. No response to ephedrine and phenylephrine. Past anesthesia for skin grafting 9 days back: induced with propofol, fentanyl and rocuronium. Developed profound hypotension, no palpable pulses; received CPR, defibrillation (shock), ECMO and IABP support. Weaned of ECMO and IABP in POD 1 and 2.	Sugammadex (200 mg) administered 6 minutes after rocuronium. Rapid improvement in hemodynamic status. Tracheostomy successfully performed.	Elevated serum tryptase level. BAT strongly to rocuronium.
Kim SM et al. ²⁴	75-year-old 51 kilogram woman for decompressive lumbar laminectomy and interbody fusion.	Induction with propofol. Maintenance anesthesia with desflurane and remifentanyl. NMB with rocuronium. Antibiotic (cefazolin) administered. Ten minutes later, hypotension. No response to ephedrine, phenylephrine, isotonic fluids, dexamethasone, pheniramine, and epinephrine bolus and infusion.	Sugammadex 200 mg (4 mg/kg) administered 80 minutes after rocuronium. Hemodynamic status stabilized.	Tracheal extubation 30 minutes after arrival in the ICU. No need for vasoactive agents. Discharged to home. Intradermal skin testing was markedly positive for rocuronium.

NMB = neuromuscular blockade; ACLS = advanced cardiac life support; ROSC = return of spontaneous circulation; ETT = endotracheal tube; ICU = intensive care unit; BAT = Basophil activation test, ICU= Intensive care unit; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump.