Successful management of rocuronium-induced anaphylaxis with sugammadex: A case report

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Abstract
Although anaphylaxis during anaesthesia is a rare event, neuromuscular blocking drugs are responsible for 62% of anaesthesia-related anaphylaxis. However, sugammadex, a modified gamma-cyclodextrin, can encapsulate rocuronium molecules and cause the rapid reversal of the neuromuscular blockade. A 68-year-old man who presented for a radical prostatectomy was induced with IV fentanyl/propofol/rocuronium. He had not received rocuronium previously but had received cisatracurium. Shortly after anaesthesia, the patient’s heart rate abruptly increased, and systolic blood pressure (SBP) dropped to 40 mm Hg. Despite cardiopulmonary resuscitation and intensive management, his haemodynamic stability did not improve until he received IV sugammadex, 200 mg. Intradermal skin tests showed he was positive for cisatracurium, rocuronium and succinylcholine. The patient was suspected to have cross-reactivity of rocuronium with cisatracurium. This case highlights the potential benefit of sugammadex as an adjunct to conventional measures during rocuronium-induced anaphylaxis.

Keywords
Anaphylaxis, neuromuscular blocking agent, rocuronium, sugammadex, intradermal skin test

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**Introduction**

Anaphylaxis during anaesthesia is a rare event that has been estimated to occur in 1 in 10,000–20,000 cases. Importantly, neuromuscular blocking drugs (NMBDs) are responsible for 62% of anaesthesia-related anaphylaxis cases. In a recent study, the incidence of intraoperative anaphylaxis was 1:2499 for rocuronium and 1:2080 for succinylcholine whereas for atracurium it was 1:22,451.

Anaphylaxis is associated with increased perioperative morbidity and accounts for nearly 1500 deaths every year in the United States. Sugammadex is a modified gamma-cyclodextrin that has a high affinity for the steroidal NMBDs rocuronium and vecuronium. It can form a tight inclusion complex with rocuronium or vecuronium, thereby inactivating the effects of these steroidal NMBDs and causing rapid reversal of neuromuscular blockade. We report here, a case of severe rocuronium-induced anaphylaxis that was successfully treated with sugammadex in a patient with possible cross-reactivity to cisatracurium.

**Case Report**

A 68-year-old man with a history of type 2 diabetes mellitus, hypertension, obstructive sleep apnoea syndrome, benign prostatic hyperplasia and prostate adenocarcinoma presented for robotic-assisted radical prostatectomy. His height and weight were 153 cm and 60 kg, respectively. He had undergone uvulopalatopharyngoplasty 13 years previously and microlaryngeal surgery 12 years previously. The NMBD used for induction and maintenance during those two procedures was cisatracurium. No perioperative complications were observed during those two operations or hospital stays.

On the day of the prostatectomy, general anaesthesia was induced by intravenous (IV) administration of glycopyrrolate (0.2 mg), fentanyl (100 mcg), lidocaine (40 mg), propofol (100 mg) and rocuronium (60 mg). Bilateral clear breath sounds were noted on chest auscultation. After confirming correct endotracheal tube position, general anaesthesia was maintained with 2% sevoflurane in 40% oxygen and 60% air. The patient was ventilated with a tidal volume of 500 ml at a respiratory rate of 12 breaths/min. Peak inspiratory pressure was 15 cm H₂O and the end-tidal CO₂ was 32 mm Hg. A central venous catheter was inserted into the right internal jugular under ultrasound guidance. Arterial catheterization was performed at the right radial artery and was connected to a FloTrac/Vigileo™ system (Edwards Lifesciences, Irvine, CA, USA).

Unexpectedly, 20 minutes after induction, the patient’s heart rate abruptly increased from 75 to 120 beats/per/min, and his systolic blood pressure (SBP) dropped from 100 to 80 mm Hg. The patient’s cardiac output was 4.0 l/min, and stroke volume variation was 23%. The sevoflurane concentration was reduced to 1%. Although fluid challenge with lactated Ringer’s solution (250 ml) and isotonic saline (250 ml) as well as deep Trendelenburg position were applied, the patient’s SBP dropped to 40 mm Hg. Peak inspiratory pressure increased to 34 cm H₂O and end-tidal CO₂ decreased to 19 mm Hg. Meanwhile, chest auscultation showed left side expiratory wheezing and bilateral coarse breath sounds. However, there was no cutaneous reaction over the patient’s face, trunk or extremities. Increasing doses of ephedrine (8, 12 and 16 mg) followed by
norepinephrine (20 mcg) were administered intravenously but had minimal effect. Because of profound hypotension and presence of pulseless electrical activity 25 minutes after induction, two doses of epinephrine were administered (0.2 and 0.8 mg) followed by cardiac massage.

After one minute of cardiac massage and the administration of an additional dose of epinephrine (1mg), the patient’s heart rate reached 150 bpm and SBP was approximately 50–60 mm Hg. Hydrocortisone (200mg) was administered intravenously as an adjunct and epinephrine was administered intermittently, but the SBP could only be maintained at approximately 60 mm Hg. The patient’s cardiac output was 4.0 l/min, and the stroke volume variation was 30%. Repeated chest auscultation revealed bilateral expiratory wheezing in all lung fields with a peak inspiratory pressure of 44 cm H₂O.

A mixture of fenoterol (200 mcg) and terbutaline (5mg) were administered by inhalation via the endotracheal tube and peak inspiratory pressure decreased to 23 cm H₂O. The arterial blood gas data showed respiratory acidosis (pH, 7.22; partial pressure of carbon dioxide (PₐCO₂), 58 mm Hg; bicarbonate (HCO₃⁻), 23.7 mmol/l) and an increased gap between PₐCO₂ and end-tidal CO₂ (22 mm Hg) which could have been attributed to bronchospasm. Serum glucose, sodium (Na⁺), potassium (K⁺), calcium (Ca²⁺) and partial pressure of arterial oxygen (PₐO₂) were within normal limits (glucose, 153 mg/dl; Na⁺, 137 mmol/l; K⁺; 4.3 mmol/l; Ca²⁺, 1.18 mmol/l; PₐO₂, 238 mm Hg). The ventilator settings were adjusted to a tidal volume of 600 ml and a respiratory rate of 14 breaths/min. Ultrasonography of the thorax showed bilateral normal pleural sliding without evidence of pneumothorax. In addition, transoesophageal echocardiography revealed normal left and right ventricular contractility and trivial mitral regurgitation. Left ventricular ejection fraction was 78.8% and SBP was maintained at approximately 60–70 mm Hg during epinephrine (0.20 mcg/kg/min) and norepinephrine infusions (0.20 mcg/kg/min). No urticaria or angioedema was noted throughout the episode.

Because optimal blood pressure could not be achieved, at 80 minutes after induction we administered IV sugammadex (200mg). Shortly thereafter, the patient’s SBP increased to 100 mm Hg and remained consistently stable. The epinephrine infusion was tapered down, and the patient’s SBP was maintained at approximately 90 mm Hg with the existing norepinephrine infusion. As a result of this adverse reaction to anaesthesia, the operation was cancelled and the endotracheal tube was removed in the operating room following a negative cuff-leak test. The norepinephrine infusion was tapered down in the post-anaesthesia care unit. The patient was sent to surgical intensive care unit for one day followed by transfer to a hospital ward. The timeline of the patient’s clinical course is depicted in Figure 1.

Following discharge, the patient was referred to a dermatologist for a survey of drug allergies. His serum immunoglobulin (Ig) E antibody levels were elevated (1600 IU/ml on Day 11 after the anaphylactic episode). Histamine release test showed a positive reaction for cisatracurium, but the basophil activation test was negative. Although a skin prick test was negative, a drug allergy intradermal test showed positive reactions for cisatracurium (0.5 cm infiltration after 15 minutes at a 0.1 dilution), rocuronium (0.3 cm infiltration after 15 minutes at a 0.1 dilution) and succinylcholine (0.5 cm infiltration after 15 minutes at a 0.1 dilution). The patient’s prostate
cancer was treated conservatively at the urology outpatient department.

Written informed consent for the publication of this report was obtained from the patient and this report adheres to CARE guidelines.10

Discussion

Perioperative anaphylactic reactions are critical and potentially life-threatening events that affect multiple organ systems.11,12 They are the result of the response to a pre-sensitized allergen, and result in the massive release of mediators from mast cells or circulating basophils mediated by the cross-linking of IgE antibodies.11,13 The activation of mediators such as complement and/or bradykinin cascade directly activates mast cells and/or basophils and thus causes anaphylactoid reactions. The clinical features of anaphylactic and anaphylactoid reactions are similar and indistinguishable.11 The clinical manifestation of perioperative anaphylaxis is diverse and ranges from mild to severe symptoms which can include cutaneous, respiratory, circulatory and central nervous changes, including cardiac arrest.8,14 A four-grade severity scale has been used to categorise the degree of the anaphylactic reaction: grade 1, anaphylaxis with cutaneous signs; grade 2, anaphylaxis with measurable but not life-threatening symptoms, including cardiovascular reaction (tachycardia, hypotension), gastrointestinal disturbance (nausea)

Figure 1. Timeline of the patient’s clinical course including medications, clinical events and vital signs. Abbreviations: BPM, beats per minute; CPCR, cardiopulmonary cerebral resuscitation; EPI, epinephrine; FEN, fentanyl; GA, general anaesthesia; GLY, glycopyrrolate; HC, hydrocortisone; HR, heart rate; Lido, lidocaine; NE, norepinephrine; OP, operation; PACU, post anaesthesia care unit; PEA, pulseless electrical activity; PPF, propofol; ROC, rocuronium; SBP, systolic blood pressure; SEVO, sevoflurane; SUG, sugammadex.
and respiratory disturbance (cough or mechanical ventilation difficulty); grade 3, anaphylaxis with life-threatening reactions, including severe bronchospasm or cardiovascular collapse; grade 4, anaphylaxis with cardiac and/or respiratory arrest.15–21

In this present case, the patient developed grade 4 anaphylaxis following rocuronium administration. The patient had no previous exposure to rocuronium and cisatracurium was the only NMBD used previously, so the tentative diagnosis was either anaphylactoid reaction to rocuronium, or, anaphylactic reaction to rocuronium with cross-reactivity to cisatracurium. This notion was supported by the subsequent drug allergy intradermal test showing a positive reaction to rocuronium and cisatracurium. The patient’s profound hypotension was maintained despite the administration of epinephrine and adjuncts but was promptly reversed by sugammadex.

IgE plays a crucial role in bestowing immunological specificity to immune effector cell activation in anaphylaxis as well as other allergic diseases.22–26 Among all the antibody isotypes, most IgE remains in the tissue, and free serum IgE has the lowest concentration (50 ng/ml in healthy subjects vs. 3 mg/ml for IgA1 and 9 mg/ml for IgG1).23 Serum IgE levels increase during allergic reactions.24,27 In this present case, the patient’s IgE level (1600 IU/ml) was much higher than the reference value, which suggests that he had an allergic reaction to rocuronium. Basophil activation tests using flow cytometry are often used in the investigation of IgE-mediated allergy to drugs as well as non-IgE-mediated anaphylactoid reactions.28 We suggest that the negative results for the basophil activation test in this case may have been due to non-responding or false-negative results. For example, recent exposure to the allergen may result in a temporary refractory period of the cells and/or transiently reduced allergen-specific IgE (circulating and membrane-bound) which can cause false-negative results.28 Based on the patient’s intradermal test results, he may have had an anaphylactic reaction due to cross-reactivity between rocuronium and cisatracurium. Indeed, patients allergic to rocuronium have been reported to have cross-reactivity to succinylcholine and cisatracurium at rates of 44% and 5%, respectively.29

The usefulness of sugammadex in improving rocuronium-induced anaphylaxis is still controversial. Similar to the results of our study, several previous case reports have found positive results.30–33 In addition, a review of 11 cases from seven different countries showed that sugammadex improved recovery from rocuronium-induced anaphylaxis.34 However, other case studies have reported that sugammadex does not modify the clinical course of a suspected rocuronium-induced hypersensitivity.35–37 By encapsulating rocuronium in the plasma, it is reasonable to suggest that sugammadex may be beneficial in the reversal of anaphylaxis caused by the steroidal NMBD.38–40 In addition to the rapid blockade of the free form of rocuronium, it has been speculated that the affinity of sugammadex for rocuronium could exceed the affinity of the NMBD for cell-bound IgE antibodies.32 However, in vivo or in vitro studies to support this speculation are lacking. Further investigations that address the competition between sugammadex and IgE antibodies for rocuronium may be helpful in clarifying underlying mechanisms. Moreover, sugammadex alone has been reported to be associated with allergic reactions.8

In conclusion, we report here a rare case of severe rocuronium-induced anaphylaxis that was successfully treated with sugammadex in a patient with possible cross-reactivity to cisatracurium. This case highlights the potential beneficial effect of sugammadex as an adjunct to conventional...
measures during rocuronium-induced anaphylaxis. New, prospective, well controlled studies are required to establish the exact usefulness of sugammadex in the treatment of anaphylaxis caused by NMBDs.

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The authors declare that there are no conflicts of interest.

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**References**

1. Fisher MM and Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Reanim* 1993; 12: 97–104.

2. Laxenaire MC. [Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994–December 1996)]. *Ann Fr Anesth Reanim* 1999; 18: 796–809.

3. Reddy JI, Cooke PJ, Van Schalkwyk JM, et al. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. *Anesthesiology* 2015; 122: 39–45.

4. Mertes PM, Ebo DG, Garecz T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. *Br J Anaesth* 2019; 123: e16–e28.

5. Gaeta TJ, Clark S, Pelletier AJ, et al. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol* 2007; 98: 360–365.

6. Neugut AI, Ghatak AT and Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med* 2001; 161: 15–21.

7. Kang E, Lee BC, Park JH, et al. The Relationship between the Timing of Sugammadex Administration and the Upper Airway Obstruction during Awakening from Anesthesia: A Retrospective Study. *Medicina (Kaunas, Lithuania)* 2021; 57: 88.

8. Arslan B, Sahin T and Ozdogan H. Sugammadex and anaphylaxis: An analysis of 33 published cases. *J Anaesthesiol Clin Pharmacol* 2021; 37: 153–159.

9. Naguib M. Sugammadex: Another milestone in clinical neuromuscular pharmacology. *Anesth Analg* 2007; 104: 575–581.

10. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.

11. Lagopoulos V and Gigi E. Anaphylactic and anaphylactoid reactions during the perioperative period. *Hippokratia* 2011; 15: 138–140.

12. Pichler WJ (ed): *Drug Hypersensitivity.* Basel, Karger, 2007: pp 204–215.

13. Doan T, Melvold R, Viselli S, et al. Chapter 14 Hypersensitivity Reactions. *Lippincott's Illustrated Reviews: Immunology* 2e. 2012. pp207–226

14. Harper NJ, Dixon T, Dugué P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; 64: 199–211.

15. Mertes PM, Laxenaire MC and Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. *Anesthesiology* 2003; 99: 536–545.

16. Ring J and Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet (London, England)* 1977; 1: 466–469.

17. Reisacher WR. Anaphylaxis in the operating room. *Curr Opin Otolaryngol Head Neck Surg* 2008; 16: 280–284.

18. Takazawa T, Mitsuhashi H and Mertes PM. Sugammadex and rocuronium-induced anaphylaxis. *J Anesth* 2016; 30: 290–297.
20. Ring J, Behrendt H and De Weck A. History and classification of anaphylaxis. *Chem Immunol Allergy* 2010; 95: 1–11.
21. Ring J, Grosber M, Brockow K, et al. Anaphylaxis. *Chem Immunol Allergy* 2014; 100: 54–61.
22. Reber LL, Hernandez JD and Galli SJ. The pathophysiology of anaphylaxis. *J Allergy Clin Immunol* 2017; 140: 335–348.
23. Dullaers M, De Bruyne R, Ramadani F, et al. The who, where, and when of IgE in allergic airway disease. *J Allergy Clin Immunol* 2012; 129: 635–645.
24. Galli SJ and Tsai M. IgE and mast cells in allergic disease. *Nat Med* 2012; 18: 693–704.
25. Oettgen HC. Fifty years later: Emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases. *J Allergy Clin Immunol* 2016; 137: 1631–1645.
26. Gould HJ and Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008; 8: 205–217.
27. Platts-Mills TAE, Schuyler AJ, Erwin EA, et al. IgE in the diagnosis and treatment of allergic disease. *J Allergy Clin Immunol* 2016; 137: 1662–1670.
28. Ebo DG, Sainte-Laudy J, Bridts CH, et al. Flow-assisted allergy diagnosis: current applications and future perspectives. *Allergy* 2006; 61: 1028–1039.
29. Sadleir PH, Clarke RC, Bunning DL, et al. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth* 2013; 110: 981–987.
30. McDonnell NJ, Pavy TJ, Green LK, et al. Sugammadex in the management of rocuronium-induced anaphylaxis. *Br J Anaesth* 2011; 106: 199–201.
31. Barbosa FT and Da Cunha RM. Case of anaphylaxis induced by rocuronium treated with sugammadex. *Rev Bras Anestesiol* 2012; 62: 538–542.
32. De La Cruz I, Errando C and Calaforra S. Treatment of Anaphylaxis to Rocuronium with Sugammadex: A Case Report with Bronchospasm as the Only Symptom. *Turk J Anaesthesiol Reanim* 2019; 47: 69–72.
33. Takise Y, Kato J, Suhara T, et al. Life-threatening rocuronium-induced anaphylactic shock without cutaneous manifestations successfully reversed with sugammadex: a case report. *JA Clin Rep* 2020; 6: 95.
34. Baldo BA and McDonnell NJ. Sugammadex and anaphylaxis in the operating theater. *Rev Esp Anestesiol Reanim* 2014; 61: 239–245.
35. Hakozaki T and Murakawa M. Rocuronium-induced anaphylaxis not improved by low dose sugammadex: a case report. *Anaesth Intensive Care* 2016; 44: 522.
36. Binczak M, Fischler M and Le Guen M. Efficacy of Sugammadex in Preventing Skin Test Reaction in a Patient With Confirmed Rocuronium Anaphylaxis: A Case Report. *A&A practice* 2019; 13: 17–19.
37. Platt PR, Clarke RC, Johnson GH, et al. Efficacy of sugammadex in rocuronium-induced or antibiotic-induced anaphylaxis. A case-control study. *Anaesthesia* 2015; 70:1264–1267.
38. Jones PM and Turkstra TP. Mitigation of rocuronium-induced anaphylaxis by sugammadex: the great unknown. *Anaesthesia* 2010; 65: 89–90; author reply
39. Baldo BA, McDonnell NJ and Pham NH. The cyclodextrin sugammadex and anaphylaxis to rocuronium: is rocuronium still potentially allergenic in the inclusion complex form? *Mini Rev Med Chem* 2012; 12: 701–712.
40. Baldo BA, McDonnell NJ and Pham NH. Drug-specific cyclodextrins with emphasis on sugammadex, the neuromuscular blocker rocuronium and perioperative anaphylaxis: implications for drug allergy. *Clin Exp Allergy* 2011; 41: 1663–1678.