

# The First Case Report of Anaphylaxis Caused by the Inclusion Complex of Rocuronium and Sugammadex

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A 50-year-old man developed a severe anaphylactic reaction shortly after the administration of sugammadex at the end of an uneventful laparoscopic appendectomy. Subsequent skin testing was negative to all agents to which the patient was exposed including sugammadex. Because of the temporal relationship to the administration of sugammadex, further skin testing was performed with premixed sugammadex and rocuronium that produced a markedly positive response. This is the first case report of anergy to the individual components but sensitivity to the inclusion complex of rocuronium and sugammadex. Written informed consent was obtained from the patient for skin testing, photography, laser perfusion imaging, and publication of this case report. (A&A Case Reports. 2016;XXX:00–00.)

Sugammadex is a  $\gamma$ -cyclodextrin that selectively binds to nondepolarizing aminosteroid neuromuscular blocking drugs (NMBDs), forming a host–guest complex.<sup>1,2</sup> Its increasing frequency of use across many countries is changing modern anesthetic practice by facilitating the rapid, predictable reversal of muscle paralysis by agents such as rocuronium and vecuronium. Since its introduction into clinical practice, multiple case reports have emerged documenting episodes of sugammadex hypersensitivity,<sup>2–5</sup> leading to further investigation into its safety profile and delays by the US Food and Drug Administration for approval of its use, which was finally obtained in December 2015.

We have described, in a previous study, patients with a history of anaphylaxis to sugammadex who reacted to free sugammadex on intradermal testing but did not react to a sugammadex–rocuronium complex.<sup>2</sup> In a separate study, rocuronium-sensitive patients did not react to a rocuronium–sugammadex complex.<sup>6</sup> Based on the mechanism of action of sugammadex, it has been suggested that the encapsulation of rocuronium results in the occupational or conformational change of the allergenic epitopes of the individual drugs forming a nonreactive complex that would otherwise bind to IgE.<sup>1</sup> This case report demonstrates that it is possible to be nonallergic to both sugammadex and rocuronium but allergic to the inclusion complex of the 2 drugs. Failure to test with this host–guest complex in the investigation of an anaphylactic event during anesthesia in which sugammadex has been used may lead to inability to correctly diagnose the cause.

## CASE HISTORY

A 50-year-old, 95-kg man was anesthetized for a semiurgent laparoscopic appendectomy. He did not have any history

of significant medical conditions or drug allergies and took no regular medications, and several previous general anesthetics had been uncomplicated. Induction and maintenance of anesthesia throughout the surgery was uneventful. Medications received included fentanyl, propofol, suxamethonium, rocuronium, Tazocin EF (piperacillin/tazobactam; Pfizer Australia, West Ryde), dexamethasone, granisetron, parecoxib, chlorhexidine/alcohol skin preparation to the surgical site, and bupivacaine/adrenaline to the skin wounds. Anesthesia was maintained with sevoflurane. Because of residual neuromuscular blockade at the end of the case, 200 mg (2 mg/kg) sugammadex was administered intravenously, and he was transferred to his ward bed for extubation. During the transfer, monitoring of the electrocardiogram and blood pressure was discontinued but pulse oximetry remained in place. Immediately after transfer, he coughed briefly on the endotracheal tube and a fall in peripheral oxygen saturation (SpO<sub>2</sub>) to 91% was noted. There was no obvious change in respiratory compliance or presence of wheeze, swelling, or erythema. His SpO<sub>2</sub> transiently improved with manual ventilation before a rapid fall in both SpO<sub>2</sub> and end-tidal carbon dioxide concentration. Noninvasive hemodynamic monitoring was then reconnected, showing further evidence of cardiovascular collapse with an unrecordable blood pressure and bradycardia (heart rate, 40–50 beats/min). This was treated with titrated intravenous boluses of metaraminol (total 10 mg) and adrenaline (total 1 mg) as well as 3000 mL compound sodium lactate fluid. Because a carotid pulse was present on manual palpation, external chest compressions were not started. After approximately 20 minutes, his condition stabilized and he received 100 mg hydrocortisone. He was started on an adrenaline infusion to maintain a mean arterial pressure >75 mm Hg and transferred to the intensive care unit, where he was extubated 8 hours later. He developed mild periorbital swelling, but the remainder of his hospital admission was otherwise uneventful. Serum mast cell tryptase levels were elevated at 60  $\mu$ g/L at 1 hour, 22.8  $\mu$ g/L at 4 hours, and 6.1  $\mu$ g/L at 24 hours postevent (upper limit of reference range, 11.4  $\mu$ g/L).

He was reviewed at the West Australian Anaesthetic Adverse Drug Reaction Clinic 6 weeks after this event. He reported a history of childhood asthma, seasonal hayfever, and mild dermatitis. He was sensitive to lemon flavoring in food and cat hair.

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Intradermal skin testing was conducted with positive and negative controls according to the Australian and New Zealand Anaesthetic Allergy Group guidelines. All pharmaceutical agents to which he was exposed were tested including fentanyl, suxamethonium, propofol, rocuronium, piperacillin, tazobactam, granisetron, dexamethasone, parecoxib, sugammadex, chlorhexidine, povidone iodine, lidocaine, ropivacaine, bupivacaine, and gelofusine. Given the temporal relationship between sugammadex administration and the reaction, we performed further intradermal testing to more concentrated sugammadex at 1:10 (10 mg/mL) and 1:1 dilutions (100 mg/mL). Again, the testing was negative.

We then tested the complex of sugammadex and rocuronium. This was performed by mixing equal volumes of rocuronium at 1:500 dilution (0.02 mg/mL) with sugammadex 1:50 (2 mg/mL). This solution, therefore, contained rocuronium at 1:1000 and sugammadex at 1:100 dilutions, both of which had proven to be nonirritant. When injected intradermally, this produced a strongly positive result with a 16 × 10-mm wheal and surrounding flare when measured at 20 minutes.

The patient returned to the clinic for further testing 2 weeks later. Negative intradermal tests to rocuronium and sugammadex were reproduced. In addition, the alternative muscle relaxants were tested including vecuronium, pancuronium, atracurium, cis-atracurium, and suxamethonium, all of which produced negative results.

To further assess his reaction to the complex of steroidal muscle relaxants and sugammadex, combinations of the drugs were tested. The first was to reproduce the initial test (equal volumes of rocuronium at 1:500 dilution with sugammadex 1:50). This again produced a markedly positive skin response both on visual inspection and with laser speckle perfusion imaging (FLPI; Moor Instruments Ltd, Axminster, Devon, UK). A second intradermal test was performed with vecuronium and sugammadex mixed before testing with the final concentration of each drug currently recommended for intradermal skin testing (equal volumes of vecuronium at 1:500 dilution and sugammadex 1:50). This also produced a positive result with a wheal in excess of 10 mm (Figure).

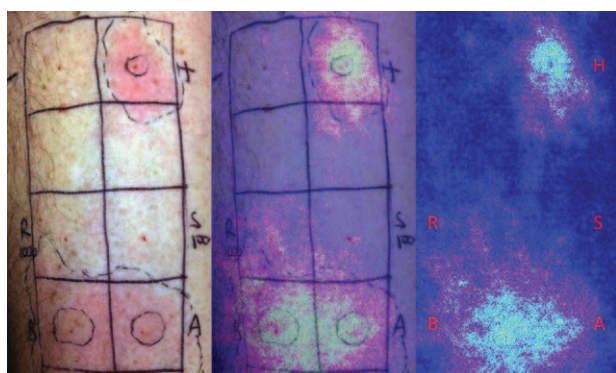


**Figure.** Volar surface of the right forearm. Laser speckle image (right) and photograph (left) of intradermal tests of 0.01 mg/mL rocuronium (R), 1 mg/mL sugammadex (S), vecuronium premixed with sugammadex (A), rocuronium premixed with sugammadex (B), and histamine positive control (H). The central image is a composite with the photograph superimposed over the laser speckle image.

Specific IgE was measured for suxamethonium, morphine, rocuronium, and pholcodine all of which had levels <0.35 kU/L, which is interpreted as a negative result. A baseline mast cell tryptase was normal (2.9 µg/L). The patient was advised that anesthesia including steroidal-based neuromuscular blocking drugs was quite safe but alternatives to sugammadex should be used for reversal.

## DISCUSSION

Because of its rapid onset and efficient reversal of effect by sugammadex, rocuronium has become the most widely used relaxant in many parts of the world although there are reports of a higher rate of anaphylaxis compared with vecuronium and benzyloisoquinoline-based drugs such as atracurium.<sup>7,8</sup> It is notable that anaphylaxis to NMBDs has not been as significant an issue in the United States as in many European countries, Australia, and New Zealand. The regional variability in the prevalence of anaphylaxis to rocuronium has led to speculation that exposure to environmental sensitizers such as pholcodine are responsible.<sup>9</sup> After a number of rejections since 2008, in part because of concerns about its allergic potential, the US Food and Drug Administration finally approved the use of sugammadex for the reversal of NMBDs in mid-December 2015. With the imminent widespread use of this newly available drug, it is important for anesthesiologists to be aware that anaphylaxis maybe triggered by both free sugammadex and by the sugammadex-rocuronium complex. During the investigation of any anaphylactic event occurring immediately after the administration of sugammadex, it is essential when skin testing to use both the free drug and its complex with rocuronium.

We considered the need for an alternate NMBD such as vecuronium that could be reversed by sugammadex in this patient. The negative skin test confirms that this drug would be tolerated, but again the complex formed with sugammadex generated a markedly positive skin test response.

This individual had not previously been exposed to sugammadex and therefore had likely been sensitized to the responsible allergen through exposure to cyclodextrins in foods, where it is commonly used as a carrier for flavoring, vitamins, polyunsaturated fatty acids, and other ingredients<sup>10</sup> or as a pharmaceutical excipient. It is notable that there was a history of allergy to citrus-flavored food and drink that frequently contains crosslinked cyclodextrin polymers to remove bitter components such as limonin or naringin. This is consistent with previous case reports, in which anaphylaxis to sugammadex occurred on its first administration.

Recognition of cardiovascular collapse may have been delayed in this case because of the lack of hemodynamic monitoring during patient transfer immediately after administration of sugammadex. However, the fall in oxygen saturations was noted within 2 minutes of drug administration and, in conjunction with the patient coughing, may have been an early sign of anaphylaxis.

## CONCLUSIONS

It is now well recognized that individually both rocuronium and sugammadex can trigger an anaphylactic reaction. We have previously reported a case of anaphylaxis caused

by sugammadex confirmed by a positive intradermal test, but testing with the rocuronium–sugammadex inclusion complex resulted in a complete absence of response. This is the first recorded case in which the inclusion complex has been shown to be responsible for triggering an anaphylactic reaction. There is indirect evidence in this case report that supports the concept of environmental sensitization by exposure to cyclodextrins in foods or pharmaceuticals. ■■

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