

Intraoperative anaphylaxis to sugammadex and a protocol for intradermal skin testing

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SUMMARY

Sugammadex is a selective binding agent for aminosteroid neuromuscular blockers whose use is increasing in anaesthetic practice. We present three cases of severe anaphylaxis coincident with sugammadex administration. Subsequent intradermal testing confirmed sugammadex as the triggering agent, with all patients having positive skin responses to a 1:100 dilution of the standard 100 mg/ml solution and two out of three having a positive response to a 1:1000 dilution. As all patients were administered sugammadex to reverse neuromuscular blockade with rocuronium, we considered that sugammadex–rocuronium complexes were a potential unique allergen. In the two patients who were additionally tested with a rocuronium–sugammadex (3.6:1 molecular ratio) mixture, the wheal-and-flare response was significantly attenuated.

Key Words: sugammadex; anaphylaxis, allergy, skin-testing protocol

Sugammadex is a selective binding agent for aminosteroid, non-depolarising neuromuscular blocking agents. We present three cases of severe intraoperative anaphylaxis that had the atypical feature of occurring toward the end of the anaesthetic procedure, coincident with the administration of sugammadex. Intradermal testing was conducted according to standard protocols, with 0.02 ml of dilute potential triggers injected with a 25-gauge hypodermic needle, producing a 3 to 4 mm intradermal bleb. All three patients were skin-tested four to eight weeks after the intraoperative reaction. A positive test was considered to be a wheal-and-flare response with a wheal diameter of at least 8 mm at 20 minutes. We routinely monitor the flare reaction with a laser speckle perfusion imager (FLPI; Moor Instruments, Wilmington, DE, USA), although this is for our research purposes only. The standard formulation of pharmaceutical agents is described with the dilution by 0.9% saline for intradermal testing in brackets. All patients provided written consent for publication.

Case 1

A 29-year-old, 100 kg woman was anaesthetised for elective endometrial ablation and sterilisation at a tertiary teaching hospital in Perth, Western Australia. She had undergone laparoscopic gastric band insertion twelve months earlier without complications and this procedure included the administration of rocuronium but not sugammadex. Since the procedure she had developed pill dysphagia and symptoms of gastro-oesophageal reflux disease. She did not take any regular medications and had no known drug or environmental allergies.

Anaesthesia was induced with fentanyl, propofol and rocuronium (1 mg/kg) using a modified rapid sequence technique. Following intubation, parecoxib, dexamethasone, droperidol and cephazolin were administered intravenously and vaginal povidone-iodine 10% solution was used for preparation of the surgical site. She remained haemodynamically stable throughout the surgical procedure, which was completed after 30 minutes. Due to residual neuromuscular blockade, sugammadex 200 mg (2 mg/kg) was administered intravenously and the patient transferred to a ward bed for emergence and extubation. However, within three minutes she became hypotensive (systolic blood pressure 30 to 40 mmHg) and tachycardic (heart rate 125/minute), with evidence of reduced cardiac output (low end-tidal partial pressure of carbon dioxide). There was no noted erythema or change in respiratory compliance. She was treated with aliquots of intravenous metaraminol (up to a total of 5 mg), adrenaline (up to a total

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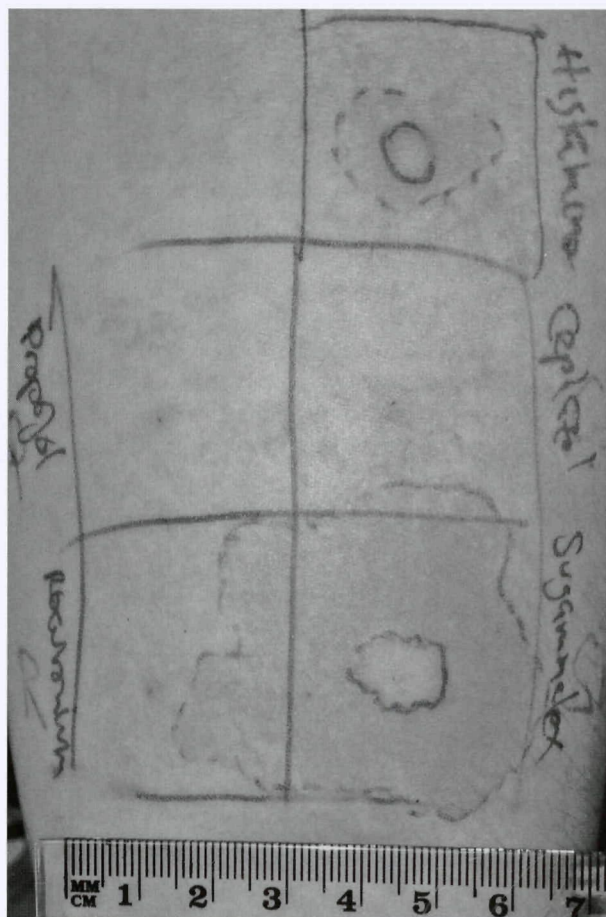


Figure 1: Case 1: Positive skin-prick test to histamine (top right box), with negative intradermal tests to propofol (middle left), rocuronium (bottom left) and cephazolin (middle right). Markedly positive intradermal test to sugammadex 1:100 (1 mg/ml; bottom right).

400 μ g) and 3000 ml of intravenous compound sodium lactate solution, and required a phenylephrine infusion to maintain her blood pressure (systolic greater or equal to 90 mmHg). Fluid and phenylephrine requirements diminished over the next two hours and she was eventually extubated two-and-a-half hours after the administration of sugammadex. She suffered generalised oedema that persisted for several days. Serum mast cell tryptase levels were 59 μ g/l at two hours, 32.2 at six hours and 6.3 at 18 hours post-event.

After informed consent and abstaining from anti-histamines, intradermal testing was conducted with dilutions of propofol 1% (1:100), rocuronium 10 mg/ml (1:100 and 1:1000), cephazolin 100 mg/ml (1:100), half-strength (5%) povidone-iodine (1:100), and sugammadex 100 mg/ml (1:100, 1:1000 and 1:10,000). Histamine 8 mg/ml skin-prick testing indicated normal skin responsiveness. All test sites were negative except the sugammadex test sites with 1:100 (see Figure 1)

and 1:1000 dilutions. A 1:10,000 dilution resulted in a wheal-and-flare reaction in which the wheal had a diameter of 7 mm, which is just below our cut-off of 8 mm for a positive reaction. To determine if the antigenic epitope was also present on the sugammadex-rocuronium complex, sugammadex (1:500) was then retested after a brief (five minute) incubation with an equal volume of rocuronium (1:50) to give equivalent dilutions of 1:1000 and 1:100, respectively. This was tested intradermally, resulting in attenuated wheal-and-flare reactions that would be considered a negative test result (see Figure 2).

Case 2

A 15-year-old girl was anaesthetised for elective adenotonsillectomy at a private hospital in Brisbane, Queensland. Her previous anaesthetic history included three uneventful general anaesthetics without exposure to sugammadex. She had suffered angioedema on exposure to peanut butter as a young child but had never experienced allergic phenomena since. Medications administered during the procedure included midazolam, fentanyl, propofol, rocuronium, morphine, parecoxib, dexamethasone, granisetron, paracetamol, cephazolin and clonidine. After extubation and incomplete treatment of residual neuromuscular blockade with neostigmine, she was administered sugammadex 100 mg. Within minutes she developed a rash covering her face, arms and trunk; facial swelling; and hypotension that required re-intubation and the administration of adrenaline boluses (total 350 μ g), then a titrated adrenaline infusion, hydrocortisone 100 mg and promethazine 50 mg. Serum tryptase was within the normal range (4.1 μ g/l at 30 minutes and 3.5 μ g/l at seven hours). Intradermal skin test results were negative to all agents tested except a 1:100 and 1:1000 dilution of sugammadex.

Case 3

A 33-year-old woman, with a past medical history of gastro-oesophageal reflux and hypothyroidism, presented for an elective laparoscopic cholecystectomy at a tertiary teaching hospital in Perth, Western Australia. Her previous surgical history included two uneventful general anaesthetics without exposure to sugammadex. She had no history of asthma or known drug or environmental allergies.

Anaesthesia was induced and surgery completed without incident. Due to residual neuromuscular blockade, 200 mg of sugammadex was administered. Almost immediately the patient developed severe bronchospasm with a rapid fall in oxygen saturation (lowest 58%). An additional dose of 200 mg of sugammadex was given and inhaled salbutamol was

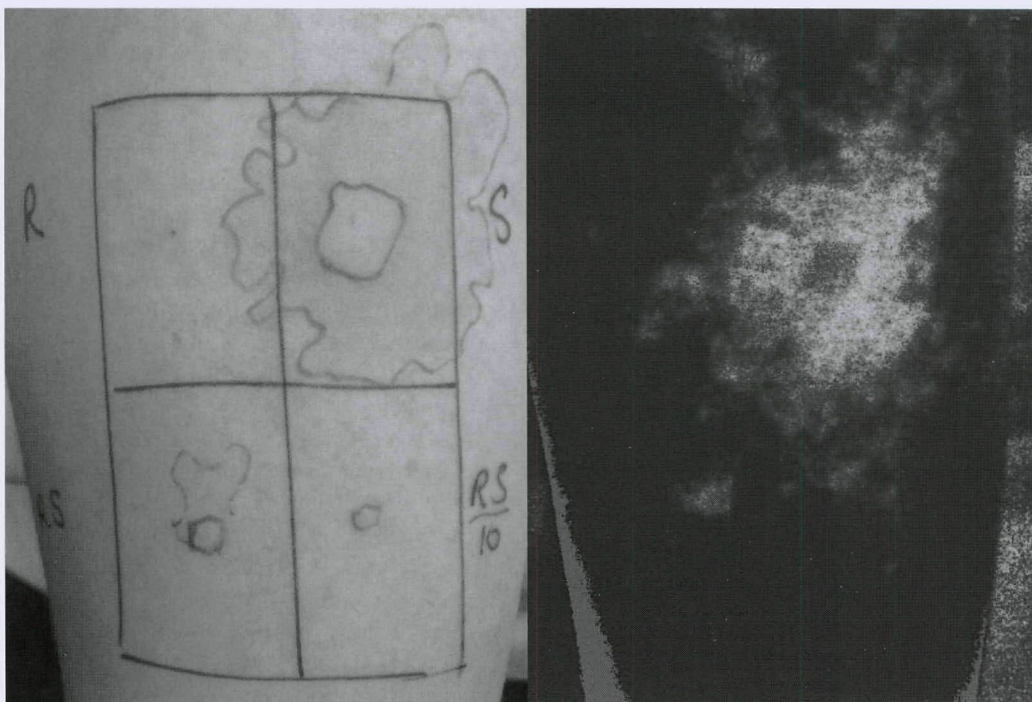


Figure 2: Case 1: Positive intradermal test to sugammadex 1:1000 (0.1 mg/ml; top right), negative to rocuronium 1:100 (0.1 mg/ml; top left) and negative to rocuronium–sugammadex mix (0.1 mg/ml of each; bottom left) and a further 1/10 dilution of the rocuronium–sugammadex mix (0.01 mg/ml of each; bottom right). FLPI laser imaging of the cutaneous blood flow demonstrates marked flare surrounding the sugammadex intradermal test, but absence of flare surrounding rocuronium or rocuronium–sugammadex mix test sites. FLPI=full field laser perfusion imaging.

administered via her endotracheal tube followed by 400 μ g of intravenous salbutamol. After several minutes her condition improved. At no point was there any cardiovascular instability or cutaneous signs of anaphylaxis. After a period of observation she was extubated and her recovery was uneventful thereafter. No mast cell tryptase assays were taken.

Intradermal skin testing was performed to propofol 1% (1:100), fentanyl 50 μ g/ml (1:100), rocuronium 10 mg/ml (1:100 and 1:1000), cephazolin 100 mg/ml (1:100), paracetamol 10 mg/ml (1:100), dexamethasone 4 mg/ml (1:100), ondansetron 2 mg/ml (1:1000) and chlorhexidine 0.2% (1:1000). The sugammadex test site was positive at a 1:100 dilution (9 mm wheal and large surrounding flare) but did not reach a positive result at the 1:1000 dilution (4 mm wheal initially, 6 mm when retested, Figure 3). All the other test sites were negative. An intradermal rocuronium and sugammadex mix (final concentrations of 1:100 and 1:1000, respectively) produced an attenuated skin response compared to that from a 1:1000 dilution of sugammadex.

DISCUSSION

Sugammadex is a cyclodextrin that is changing anaesthetic practice by allowing the rapid and predic-

table reversal of rocuronium and other aminosteroid non-depolarising neuromuscular blocking agents. Its use is increasing in many parts of the world, with the exclusion of the United States of America, where the Food and Drug Administration is continuing to review allergic and thrombotic adverse events associated with its use. We describe three patients who developed severe intraoperative anaphylaxis with a high clinical suspicion of being triggered by sugammadex due to the time-course of drug administration.

None of the patients had previously been exposed to sugammadex. This is consistent with previous case reports^{1,2}, and the responsible sensitising allergen is presumed to be cyclodextrins present in food, pharmaceuticals and cosmetics³.

Due to the short period of use of sugammadex, there are no established guidelines with respect to skin testing for hypersensitivity to sugammadex. Previous reports have used various dilutions for skin-prick testing^{1,2}. In our three cases we were able to demonstrate hypersensitivity to intradermal sugammadex at a dilution of 1:100, and two had positive results at a dilution of 1:1000, with negative skin test results to all other potential triggers. Clarke et al have observed that dilutions of 100 mg/ml sugammadex at 1:77 and 1:770 did not cause skin

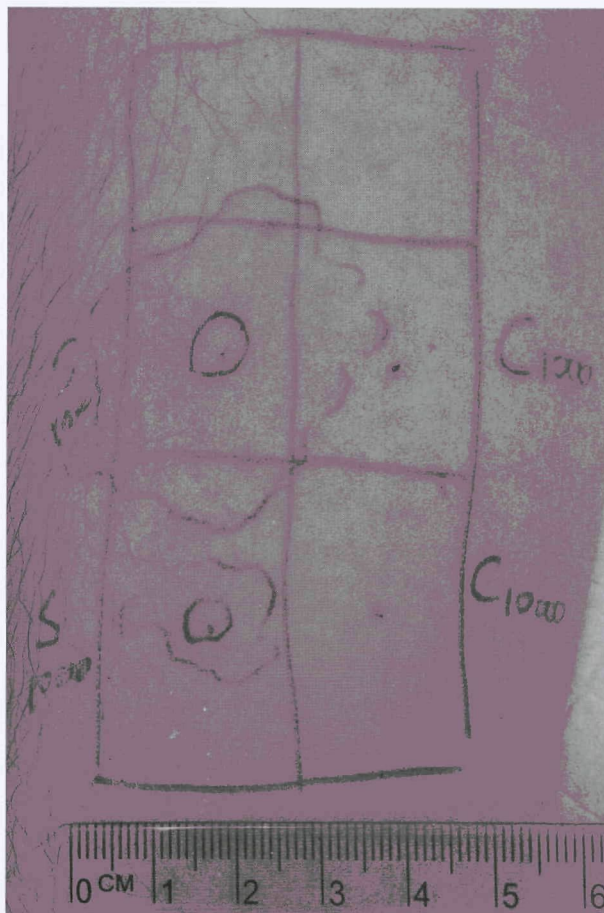


Figure 3: Case 3: Positive intradermal test to sugammadex 1:100 (1 mg/ml; middle left box). Wheal-and-flare reaction to sugammadex 1:1000 was again appreciable, but did not meet our criteria for a positive test result.

irritation or false positive reactions in 11 volunteers in a previous study⁴. Although, when tested at a 1:10,000 dilution in Case 1 and 1:1000 in Case 3, sugammadex did cause an appreciable wheal-and-flare response, it did not meet our criteria for a positive test result. A suitable intradermal skin test dilution appears to be 1:100.

As sugammadex was given to reverse the effects of rocuronium-induced neuromuscular blockade, it was expected to be present both as free molecules and as a complex with rocuronium at the time of anaphylaxis. Either or both could have been the trigger for anaphylaxis. To explore this further, in two of the three cases we mixed sugammadex (1:500 dilution) with an excess of rocuronium (1:50 dilution) to give final dilutions of 1:1000 and 1:100 respectively, which gives a final concentration of 0.1 mg/ml of each drug. In this mixture we would expect very few free sugammadex molecules, as rocuronium is present in excess with an overall 3.6:1 molecular ratio, and sugammadex binds

to rocuronium with an association constant of 1×10^7 . We were able to demonstrate that both patients tested with this protocol were reactive to free sugammadex but non-reactive to the sugammadex-rocuronium complex. Possible mechanisms by which the binding of rocuronium to sugammadex prevents immune activation may include occupation of the allergic epitope or conformational change to the allergic epitope on the sugammadex molecule that would prevent it binding to IgE. Nonetheless, it does not appear that the presence of this non-reactive complex in patients at the time of the reactions prevented anaphylaxis.

It is interesting to speculate whether the presence of the non-reactive sugammadex-rocuronium complex modified the subsequent reaction to sugammadex in these patients. In a previous study, the authors have demonstrated that rocuronium-sensitive patients do not react to the sugammadex-rocuronium complex on intradermal testing⁴. We have now also shown the reverse, that sugammadex-sensitive patients also do not react to the sugammadex-rocuronium complex. It is impossible to determine if the presence of rocuronium in these patients prior to administration of sugammadex modified the immunological response by complexing the drug into a non-reactive form, but it certainly didn't prevent a reaction. It may be that sugammadex was given in excess compared to rocuronium at the time of the reactions, or that the affinity of specific IgE for sugammadex was greater than the affinity of rocuronium for sugammadex.

CONCLUSION

In conclusion, we suggest that intradermal testing with a 1:100 dilution of sugammadex 100 mg/ml is a suitable approach to the patient who has suffered intraoperative anaphylaxis when sugammadex is considered a plausible trigger.

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