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A confirmed case of sugammadex-induced anaphylaxis in a UK hospital

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Summary

We report the first published case of confirmed anaphylaxis to sugammadex in a UK hospital. The patient was given a bolus of sugammadex at the end of surgery. Four minutes later, he developed hypotension and a widespread erythematous rash. Multiple epinephrine boluses were administered and a continuous intravenous infusion of epinephrine commenced. The patient later reported auditory awareness, which occurred while the diagnosis of anaphylaxis was being made and initial treatment initiated. Serial serum tryptase levels were consistent with a type I hypersensitivity reaction. Skin prick and intradermal testing were performed 6 months later confirming allergy to sugammadex. This case restates the potential for hypersensitivity reactions to develop following the administration of sugammadex and makes clinicians aware that such reactions may require prolonged treatment with intravenous infusions of epinephrine. Finally, this case highlights the importance of maintaining or re-establishing anaesthesia while managing the emergent situation in order to avoid unintentional awareness.

Background

Sugammadex (Bridion) is a modified γ -cyclodextrin, licensed in the UK for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults and for the routine reversal of rocuronium-induced neuromuscular blockade in children and adolescents aged 2–17 years.¹ The US Food and Drug Administration initially refused to approve the use of sugammadex due to concerns regarding hypersensitivity and anaphylactic reactions.² A systematic review published in 2014 identified 25 records of probable hypersensitivity reactions to sugammadex, including six obtained directly from the UK Medicines and Healthcare products Regulatory Agency.³ To date, however, there have been no published case reports of confirmed hypersensitivity reactions to sugammadex in UK hospitals. We report a case of a prolonged sugammadex-induced hypersensitivity reaction, confirmed by skin prick and intradermal testing.

Case presentation

A 62-year-old, 140 kg man underwent elective laparoscopic sleeve gastrectomy for morbid obesity (body mass index 47 kg m⁻²). His medical history included hypertension, type 2 diabetes mellitus and Parkinson's disease. He had previously undergone uncomplicated general anaesthesia on three occasions. The most recent of these was 4 years earlier, when he was anaesthetised for 48 hours in an intensive care unit (ICU) due to septic shock secondary to leg cellulitis. None of these anaesthetics were administered at our institution and, as such, previous anaesthetic documentation was not available at the time of the preoperative visit. There was no history of food, latex or medication allergies.

General anaesthesia was induced with propofol (150 mg) and an intravenous infusion of remifentanyl targeted to an effect site concentration of 5 ng/mL. Rocuronium (70 mg) was then administered. Anaesthesia was maintained with 6% desflurane and an intravenous infusion of remifentanyl targeted to an effect site concentration of 1 ng/mL. A subsequent dose of rocuronium (15 mg) was administered 75 min after the induction of anaesthesia, 30 min before sugammadex was given.

At the end of surgery, sugammadex (100 mg) was administered to reverse residual neuromuscular blockade. Four minutes after giving sugammadex, the patient developed hypotension (systolic arterial pressure <70 mm Hg). This failed to respond to multiple 0.5 mg boluses of metaraminol (total metaraminol 3 mg), ephedrine (9 mg) and rapid infusion of 1000 mL crystalloid. Multiple 50 μ g boluses of epinephrine were administered (total epinephrine 400 μ g) to restore the systolic arterial pressure to >100 mm Hg. A widespread erythematous rash was noted to have developed over the patient's trunk, arms and thighs. Hydrocortisone (200 mg) and chlorphenamine (10 mg) were given and the patient was commenced on a continuous intravenous infusion of epinephrine (0.05–0.3 μ g/kg/min). He was transferred to the ICU where the intravenous infusion of epinephrine was continued for 7.5 hours and the trachea was extubated 23 hours later.

Following extubation, the patient reported having been aware of the conversation that took place in the operating theatre at the time that the diagnosis of anaphylaxis was made. It is estimated that at this point, the end-tidal concentration of desflurane had reduced to approximately 1%, although the intravenous infusion of remifentanyl continued, targeted to an effect site concentration of 1 ng/mL. The patient did not report having been aware of any pain or sensation of paralysis. Shortly after establishing the diagnosis of anaphylaxis, the inspired concentration of desflurane was increased and anaesthesia was later maintained, during transfer to the ICU, using a continuous intravenous infusion of propofol.

Investigations

Serial serum tryptase levels were consistent with a type I hypersensitivity reaction (49.6 μ g/L shortly after initial cardiovascular collapse, 36.6 μ g/L after 6 hours and 15.4 μ g/L after 12 hours; normal <15 μ g/L). Skin prick and intradermal testing were performed 6 months later using the following agents: methylene blue, sugammadex, gentamicin, rocuronium and propofol. At a dilution of 1/1000, sugammadex generated a positive response on skin prick (3–4 mm weal) and intradermal testing (16 mm weal with pseudopods). Skin prick and intradermal tests for all other agents were negative.

Outcome and follow-up

The patient made a good recovery and was discharged home a week later. Routine postoperative follow-up was unremarkable. He was advised of the results of his skin prick testing and the importance of making the staff aware of his allergy should he ever require a general anaesthetic in the future.

Discussion

In summary, we report a case of confirmed anaphylaxis in a patient who received sugammadex at a dose of 0.7 mg/kg. Given that its use within UK hospitals is likely to increase over the coming years, particularly once its patent expires in 2023, it is important for clinicians to recognise the potential for hypersensitivity reactions to develop following the administration of sugammadex.⁴ This is the first published case report of a confirmed hypersensitivity reaction to sugammadex in a UK hospital. This patient satisfies the World Allergy Organization's clinical criteria for the diagnosis of anaphylaxis as he experienced a sudden decrease in arterial pressure accompanied by a widespread erythematous rash, which developed over the trunk, arms and thighs.⁵

Results of serial serum tryptase, which is the only currently available blood test for the diagnosis of acute allergic reaction, supported the diagnosis of anaphylaxis in this patient.⁶ In addition, the positive response to skin prick testing was highly suggestive of sugammadex having been the causative agent. Intradermal testing also generated a positive response, although it should be noted that intradermal tests are more sensitive but less specific than skin prick tests if the same concentration of agent is used.⁶ Alternative options for allergy testing include patch testing for T cell sensitisation, although false negatives can occur due to the low dose of drug used, as well as poor skin penetration by large drug molecules.⁶ Measurement of specific IgE in sera is possible but is currently only available for a small number of drugs and has unknown sensitivity and specificity as it requires validation against sera from definitive cases.⁶ In vitro tests including cellular allergen stimulation test, basophil histamine release tests and a basophil activation test have been proposed in the investigation of drug allergy but are not widely used in clinical practice outside of research settings.⁶ Finally, drug provocation tests may be used, particularly where other possible investigations have been exhausted and the diagnosis remains in doubt. Clearly, however, there is significant potential to precipitate an anaphylactic reaction and, as such, a precise risk–benefit assessment must be completed with the patient and referring clinician for each case.⁶

It is also important to be aware that anaphylaxis to sugammadex may require prolonged management, necessitating admission to the ICU. This patient required a protracted period (7.5 hours) of treatment with an intravenous infusion of epinephrine due to persistent hypotension. During our review of the literature, we identified only four other published case reports in which patients required continuous intravenous infusions of epinephrine following hypersensitivity reactions to sugammadex.^{7–10} The patient also reported auditory awareness, which occurred while the diagnosis of anaphylaxis was being made and initial treatment initiated. Given that sugammadex is most commonly administered at the end of surgery, by which time anaesthetic agents may have been stopped, it is important to consider the need to maintain or re-establish anaesthesia while managing the emergent situation in order to avoid unintentional awareness. Finally, it is important to recognise that, while our patient developed anaphylaxis minutes after receiving sugammadex, the potential exists for such a reaction to develop even hours after administration of the drug. As such, delayed anaphylaxis to agents administered intraoperatively should always be considered in the differential of any collapsed patient in the perioperative period.

Patient's perspective

It was quite a surprise when I briefly regained consciousness to see the surgeon standing over me, saying that the operation had gone according to plan but that I had suffered a 'severe anaphylactic reaction'. But the single action that did most to boost my self-esteem was the visit from one of the anaesthetists a day or two after I had left intensive care; we discussed the events that had occurred and reviewed my notes which made an enormous positive impact on my sense of well-being. More broadly, I am indebted to all of the medical teams who cared for me throughout the 7 days I spent in the hospital, both during my conscious hours and the times when I was unaware of their care and attention. They cannot know how much their professionalism, teamwork and prompt actions at times of crisis saved my life and enabled me to make a speedy recovery.

Learning points

- There is potential for hypersensitivity reactions to develop following the administration of sugammadex.
- Prolonged treatment with an intravenous infusion of epinephrine may be required, necessitating admission to the intensive care unit.
- As sugammadex is most commonly administered at the end of surgery, it is important to consider the need to maintain or re-establish anaesthesia while managing the emergent situation in order to avoid unintentional awareness.

Footnotes

- Contributors RO and SS planned the content and made the decision to publish the paper. RO and JH performed the background research for the paper. All authors wrote the manuscript. RO and SS revised the paper.
- Competing interests: None declared.
- Patient consent: Obtained.
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