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Case report

Three cases of suspected sugammadex-induced hypersensitivity reactions

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Editor's key points

- Sugammadex is increasingly used for the reversal of rocuronium neuromuscular block.
- Report of three cases showing evidence of an allergic response immediately after sugammadex.
- Two patients had a subsequent positive skin test to sugammadex, the third declined testing.

Summary. Neuromuscular blocking agents have been implicated in 60–70% of anaphylactic events associated with anaesthesia. We report two cases of probable hypersensitivity reaction to sugammadex and an additional suspected but less supported case of possible immune-mediated reaction or other adverse reaction. The patients were given a bolus of sugammadex 100 mg immediately before extubation. In all three patients, a possible allergic reaction was suspected within 4 min of sugammadex administration, but with different degrees of severity. Skin testing was positive in two of these patients. Hypersensitivity to sugammadex unaccompanied by cardiovascular or respiratory symptoms might be missed during the course of anaesthesia. Careful monitoring for possible allergic responses is required in patients who have received sugammadex.

Keywords: allergy; hypersensitivity; sugammadex

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Sugammadex (Bridion®) is a modified γ-cyclodextrin used for the rapid reversal of rocuronium-induced neuromuscular block by encapsulating free rocuronium molecules as inclusion complexes.[1] Neuromuscular blocking agents are the most frequently implicated drugs involved in anaphylaxis during anaesthesia.[2–4] Immunoglobulin E (IgE) antibodies to rocuronium have been reported in 48% of serum samples from patients with allergies to neuromuscular blocking agents, although only a small proportion of such IgE-positive patients will actually develop anaphylaxis.[5 6] We report three cases of suspected sugammadex-induced hypersensitivity reactions occurring between July 2010 and June 2011. These events developed immediately after the administration of sugammadex, with varying degrees of severity.

Case 1

A 41-yr-old, 53 kg female underwent elective laparoscopic distal pancreatectomy for a pancreatic tumour. Approximately 10 yr earlier, she had undergone gynaecological surgery under general anaesthesia and had not experienced any allergic events. There was no history of food, latex, or medication allergies. After the insertion of an epidural catheter, general anaesthesia was induced with propofol 70 mg and remifentanil 0.5 μg kg^{-1} min^{-1}. Rocuronium 40 mg was then administered. The anaesthesia was maintained with sevoflurane 1.5% and remifentanil 0.1–0.7 μg kg^{-1} min^{-1}. Sulbactam sodium/cefoperazone 1 g was given every 3 h during the procedure, the last occurring 145 min before sugammadex was given. At the end of surgery, sugammadex 100 mg was given to reverse the neuromuscular block. Three minutes later, the patient developed facial erythema and blepharoedema, but there was no hypotension, tachycardia, or bronchospasm. Hydroxyzine pamoate 25 mg was given i.v., and the cutaneous symptoms improved 9 min after the administration of sugammadex. Six weeks later, a skin prick test was performed. A 4 mm diameter wheal developed in response to sugammadex at a dilution of 1:10 (with a negative saline control, and a 6 mm wheal from a positive histamine control).

Case 2

A 52-yr-old, 54 kg female underwent elective thoracoscopic surgery for an anterior mediastinal tumour. She had been diagnosed with Graves' disease 4 months earlier and had been treated with levothyroxine and thiamazole for 10 days before the operation. Thyroid-stimulating hormone, free T3, and free T4 were within normal ranges up to 3 days before the operation. She had undergone breast surgery 10 yr earlier and had not experienced any allergic

events, and there was no history of food, latex, or medication allergies. After the insertion of an epidural catheter, the patient received total i.v. anaesthesia, consisting of the target-controlled infusion of propofol 2.5–3.0 μg ml^{-1} and remifentanil 0.2–0.4 μg kg^{-1} min^{-1}. Rocuronium 40 mg was given before tracheal intubation. Atropine, ephedrine, flurbiprofen axetil, fentanyl, mepivacaine, and ropivacaine were given during the procedure. At the end of surgery, sugammadex 100 mg was used to reverse the neuromuscular block. Three minutes after giving sugammadex, the patient developed hypotension (systolic arterial pressure <50 mm Hg), tachycardia (>110 beats min^{-1}), and generalized erythema. The oxygen saturation decreased from 99% to a minimum value of 83%. The peak airway pressure increased from 24 mm Hg to a maximum value of 33 mm Hg within 5 min of sugammadex administration. The patient was resuscitated with continuous i.v. infusion of epinephrine 0.03–0.1 μg kg^{-1} min^{-1} and with bolus injections of norepinephrine 50 μg (total norepinephrine 0.3 mg). Methylprednisolone 250 mg was then given. Her condition improved 42 min after commencing resuscitation. She was transferred to the intensive care unit, and the trachea was extubated 23 h later. The remainder of her hospitalization was uneventful. Four months later, a skin prick test was positive, with a 5 mm diameter wheal in response to sugammadex at a dilution of 1:1000 (with a negative saline control, and a 6 mm wheal from a positive histamine control).

Case 3

An 89-yr-old, 45 kg female underwent elective cataract surgery under general anaesthesia. She had a medical history of dementia and essential hypertension controlled with amlodipine. She had no history of general anaesthesia or allergy to any food, latex, or medications. General anaesthesia was induced with propofol 60 mg, fentanyl 100 μg, and rocuronium 30 mg for tracheal intubation, and was maintained with sevoflurane 1.0–1.5% and remifentanil 0.1–0.5 μg kg^{-1} min^{-1}. Atropine, ephedrine, and phenylephrine were given during the procedure. No additional rocuronium was needed during the 28 min procedure. The trachea was extubated 3 min after sugammadex 100 mg given in the left arm. Four minutes after extubation, she developed a wheeze on auscultation, and the oxygen saturation level decreased from 99 to 91%, and her heart rate increased to 110 beats min^{-1}. The patient developed intense erythema over her left arm 4 min after the sugammadex. A hypersensitivity reaction to sugammadex was suspected and methylprednisolone 250 mg, aminophylline 250 mg, and two puffs of procaterol were given with 5 litre min^{-1} of 100% oxygen via a facial mask; the patient's condition improved within 30 min. Skin prick testing for this patient was declined.

Discussion

Sugammadex was used during general anaesthesia in 1864 cases at our hospital between July 2010 and June 2011. These three cases of suspected hypersensitivity occurred immediately after the administration of sugammadex at doses ranging from 1.9 to 2.2 mg kg^{-1}. The reactions developed 3 min after the injection of sugammadex in two patients. In Case 3, the possibility of a non-immunological adverse reaction could not be excluded without immunological investigation with skin prick testing and/or serum IgE testing. None of these patients had received sugammadex before, although prior sensitization with other drugs, foods, or common environmental chemicals could result in similar adverse reactions due to cross-sensitivity.[7] Intraoperative anaphylaxis has been estimated to occur in between one in 3500 and one in 13 000 cases.[8] Sugammadex appears to be a safe and well-tolerated agent and is available in the European Union.[9] The most frequently reported adverse effects have been hypotension, coughing, nausea, vomiting, dry mouth, a sensation of a change in temperature, and abnormal levels of *N*-acetylglucosaminidase in the urine.[9 10] Sugammadex-related allergic reactions reportedly include flushing, tachycardia, and an erythematous rash and appear to be more frequent at higher clinical doses (16–96 mg kg^{-1}).[11 12] More recently, allergic reactions to sugammadex were observed at a lower clinical dose (3.2 mg kg^{-1}).[7] We report two cases of probable hypersensitivity reaction, and a third milder case of suspected allergic reaction or other possible non-immunological reaction, to sugammadex at doses ranging from 1.9 to 2.2 mg kg^{-1}.

A skin prick test is widely used for the diagnosis of IgE-mediated allergic reactions.[4] Although the British Society for Allergy and Clinical Immunology (BSACI) recommends using 1:10-diluted or undiluted drugs for a skin prick test,[13] we performed the test with diluting sugammadex to the concentrations of 1:1000, 1:100, or 1:10 in saline, and the test was started with the smallest concentration as described previously,[14] because of false-positive results at the 1:10-diluted or undiluted solution of the neuromuscular blocking drug. Although the positive result was obtained with 1:1000-diluted sugammadex in Case 2, we could not exclude the possibility of false-positive skin reactions. Also, it is possible that allergic individuals may have a lower drug concentration threshold for positive skin reactions.

We were unable to determine whether the suspected hypersensitivity reactions reported were IgE-mediated or non-IgE-mediated, as the serum levels for IgE antibodies specific to sugammadex were not determined. Therefore, non-specific histamine release by sugammadex, as is known to occur with opioids, for example, could not be excluded. Skin testing for other anaesthetic or antibiotic drugs was not performed in these patients. We could not exclude the possibility of late-onset allergic reactions induced by other agents, including latex, antibiotics, i.v. colloids, and Cidex OPA (used for disinfecting surgical instruments).[4]

The European Academy of Allergology and Clinical Immunology (EAACI) defines anaphylaxis as a 'severe, life-threatening, generalized or systemic hypersensitivity reaction'. Minor, localized, or non-systemic reactions are outside the definition of anaphylaxis.[4] Using the severity scale for

assessing the intensity of hypersensitivity reactions, these cases were graded as: Case 1, grade 1; Case 2, grade 3; Case 3, grade 2 (with grade 3 indicating greater severity than grade 1).[15] The severity of the clinical features differed among the cases, indicating that sugammadex may cause local or systemic level hypersensitivity or non-allergic adverse reactions.

In summary, we report two cases of probable allergic reaction and one case of possible allergic or non-allergic adverse reaction to sugammadex in patients who received sugammadex at doses ranging from 1.0 to 4.0 mg kg^{-1} during general anaesthesia. Although the severity of the suspected hypersensitivity reactions differed, they occurred within a few minutes, suggesting that a possible hypersensitivity reaction to sugammadex may occur shortly after administration. It is important to be aware of possible allergic and non-allergic adverse reactions in patients receiving sugammadex.

Declaration of interest

None declared.

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