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CASE REPORT

Allergy to low dose sugammadex

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Summary

We describe the case of a fit 17-year-old man who developed a severe allergic reaction to a low clinical dose of sugammadex (3.2 mg kg^{-1}, 200 mg intravenously), 1 min after its administration. This was manifest by an intense erythema over the anterior part of the thorax, severe lip and palpebral oedema and bilateral wheeze. On later investigation, the patient had a positive skin prick test to sugammadex (5-mm diameter response, with a negative saline control and positive histamine control of 5 mm) and no response to any other drug tested. Other diagnostic tests supported a diagnosis of allergic reaction to sugammadex.

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Sugammadex (Bridion®; Schering Plough, Kenilworth, NJ, USA) is a modified gamma-cyclodextrin in widespread use for the antagonism of the neuromuscular blockade produced by rocuronium. It is currently available in the European Union; however, in the US, the Food and Drug Administration has had concerns about its safety, specifically concerning its potential for hypersensitivity and allergic reactions [1].

Case report

A 62-kg, 170-cm, 17-year-old man, of ASA physical status 1, with no previous medical or surgical history, was having scheduled ankle surgery. After sedation with 2 mg midazolam, a sciatic nerve block was inserted for postoperative analgesia, using 30 ml levobupivacaine 0.375%. Spinal anaesthesia was then performed with 12 mg hyperbaric bupivacaine and 10 μg fentanyl. The patient described discomfort after the start of surgery, so that a laryngeal mask airway was placed, after induction of anaesthesia with 150 mg propofol and 150 μg fentanyl and 20 mg rocuronium 20 mg to facilitate ventilation of the patient's lungs. Anaesthesia was maintained by an oxygen and air mixture in a ratio of 1:1 and 0.8 MAC sevoflurane. Other drugs administrated were 2 g cefazoline, 1 g paracetamol, 50 mg dexketoprofen and 4 mg ondansetron. All were administrated without incident. At the end of surgery, 200 mg sugammadex (corresponding to 3.2 $mg.kg^{-1}$), diluted in 8 ml saline 0.9%, was injected slowly to antagonise residual neuromuscular blockade. One minute after the administration of sugammadex, the patient developed intense erythema over the anterior part of the thorax and severe lip and palpebral oedema. The patient's observations before this had been blood pressure 120–140/80–90 mmHg; heart rate 70–85 $beat.min^{-1}$ and oxygen saturation 99%. At this point, his blood pressure fell to 78/32 mmHg, a tachycardia developed of between 100–110 $beat.min^{-1}$ and oxygen saturation fell to 93–94%. Lung auscultation revealed bilateral wheeze. The patient's trachea was intubated.

Possible allergic reaction to sugammadex was suspected and treatment with 100 mg hydrocortisone, 80 mg methylprednisolone, an antihistamine (5 mg dexchlorpheniramine) and 4 puffs salbutamol was given. The patient was transferred, with his trachea intubated, to the recovery unit. His trachea was extubated

uneventfully approximately 2.75 h later, when he had no further wheeze or erythema and very little oedema.

In consultation with an allergist, the patient was investigated using our standard hospital protocol for the investigation of anaphylaxis. A comprehensive allergy history was taken from the patient and his family. This revealed some episodes of mild asthma in his past medical history, although he had had no exacerbation of his asthma in the previous 10 years. The allergist evaluated all drugs used during anaesthesia. Of these, only sugammadex gave a positive skin prick test (he had a 5-mm diameter response, with a negative saline control and a positive histamine control of 5 mm). The results of blood tests taken at less than 30 min, 1 h and 6 days, are shown in Table 1. In addition, at 1 h after the event, full blood count, activated partial thromboplastin time, prothrombin time, fibrinogen, fibrin degradation products, platelet count, glucose, urea and electrolytes, creatinine, serum alanine aminotransferase concentration and arterial blood gas were all normal. At 24 h after the event, full blood count, activated partial thromboplastin time, prothrombin time, fibrinogen, fibrin degradation products, platelet count, glucose, urea and electrolytes, creatinine, and serum alanine aminotransferase were again all normal. The episode was diagnosed as a grade-3 hypersensitivity reaction to sugammadex according to Laxenaire's classification [2]. Testing also revealed that the patient was sensitive to house dust mite (*Dermatophagoides pteronyssinus*). Being an atopic individual may have predisposed this patient to an allergy to sugammadex, a drug that is in fact, a very simple molecule.

Table 1 Results of the investigations carried out into the patient's suspected anaphylaxis event.

Time elapsed since adverse event	Test carried out	Value	Normal range
< 30 min	Histamine concentration	3.1	0–1.0 $\mu g.l^{-1}$
1h	Serum tryptase	7.85	0–11.4 $\mu g.l^{-1}$
	C1 esterase inhibitor	0.26	0.22–0.45 $g.l^{-1}$
	Complement C3	0.939	0.9–1.8 $g.l^{-1}$
	Complement C4	0.103	0.1–0.4 $g.l^{-1}$
	Total IgE	0.235	0.002–0.187 $U.l^{-1}$
	Carcino-embryonic antigen	1.6	0–5 $\mu g.l^{-1}$
6 days	Serum tryptase	6.97	0–11.4 $\mu g.l^{-1}$
	Dermatophagoides pteronyssinus	55.6	0–0 $kU.l^{-1}$
	Latex	0.01	0–0 $kU.l^{-1}$
	Total IgE	340	0–0 $kU.l^{-1}$
	Eosinophil cationic protein	59.2	0–11.3 $\mu g.l^{-1}$

Discussion

The majority of publications involving sugammadex suggest that it is a safe and well-tolerated drug [3], even in patients with renal insufficiency [4]. It has even been proposed that sugammadex could be used in the treatment of anaphylaxis to rocuronium [5]. The main adverse effect described is dysgeusia (at higher clinical doses of sugammadex), although diarrhoea [6] and a slight reduction in heart rate [7] can be observed at lower clinical doses (2–4 $mg.kg^{-1}$). The relationship between rocuronium and sugammadex and corrected QT interval has also been studied, with the conclusion that there is no association between its use and QTc prolongation [8, 9].

Studies in healthy adult volunteers have described mild allergy-like reactions including flushing, tachycardia and erythematous rash, all suggestive of hypersensitivity to sugammadex. These reactions appear to be more frequent at higher clinical doses (16–96 $mg.kg^{-1}$), although all have been self-limiting and not required treatment [9–11]. Cammu et al. [9] described episodes of mild headache, tiredness, a cold feeling at the site of injection, dry mouth, oral discomfort, nausea, increased aspartate aminotransferase and gamma-glutamyl transferase levels, and moderate injection site irritation as possibly related to sugammadex (16–32 $mg.kg^{-1}$). Peeters et al. [10] reported one case of probable hypersensitivity to sugammadex at the high-dose range (32–96 $mg.kg^{-1}$).

This is the first description of a confirmed allergic reaction at the usual lower clinical dose of sugammadex. The patient had not received sugammadex before this event. We speculate that previous sensitisation may have occurred due to the oral ingestion of cyclodextrins, molecules present in many foods. It has been calculated that a human ingests approximately 4 g of cyclodextrins per day [12]. The combination of sensitisation to cyclodextrins, in a patient with mild asthma and sensitivity to house dust mite, may have triggered this event.

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