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Letter to Editor

Anaesthesia Section

A Rare Case of Atrial Fibrillation due to Anaphylaxis to Sugammadex

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Dear Editor,

Sugammadex is a modified gamma-cyclodextrin which reverses the neuromuscular blockade of aminosteroid agents (rocuronium and vecuronium) by binding and encapsulating the amionosteroid molecule. The rocuronium/sugammadex combination has found increasing popularity in rapid sequence induction, in place of suxamethonium. Sugammadex has also been used to treat rocuronium-induced anaphylaxis [1]. The application of sugammadex for the reversal of muscle relaxants is widespread in Japan. The anaphylaxis from sugammadex in Japan is 0.02% or 1:5000 administrations [2]. This exceeds the quoted ranges for succinylcholine (1:9006) and teicoplanin (1:6101), both widely felt in the United Kingdom (UK) to be the highest risk drugs in the cupboard for perioperative anaphylaxis [3].

This letter is about a 78-year-old man, who was attended for a video-assisted thoracoscopy, drainage and insertion of PleurX catheter for mesothelioma. Previously, he had undergone open reduction and internal fixation of right radius fracture and left ankle fracture fixation, under general anaesthesia, which were uneventful. He was not a smoker, and he had no other medical history. Specifically, he had no history of asthma, but only mild atopy. He had a history of nausea and vomiting following morphine administration.

An arterial line was placed prior to induction of anaesthesia, which was achieved with midazolam, fentanyl and propofol followed by 100 mg rocuronium to facilitate tracheal intubation with a left sided double lumen tube (39Fr Shiley Endobronchial, Covidien, Ireland). One-lung ventilation was well tolerated, and anaesthesia was maintained with sevoflurane. Additional analgesia, antibiotics and antiemetics were administered throughout the procedure as per usual practice. The surgical site was prepared with alcohol in chlorhexidine. The procedure lasted 45 minutes, during which time there was no physiological derangement. At completion of surgery, there was significant residual neuromuscular blockade (one twitch on train-of-four testing). This was reversed with 200 mg sugammadex (slightly more than 2 mg/kg). Within 30 seconds of sugammadex administration, the patient started to cough and became flushed. The arterial line trace was observed to reduce over the course of less than one minute from 140/88 mmHg to a lowest reading of 35 mmHg systolic. The bed was inverted, a Senior Consultant support was called, and the patient was administered a fluid bolus of Gelofusin and repeated boluses of dilute metaraminol to a total of 3 mg. End-tidal sevoflurane at this point was around 0.3.

The patient's blood pressure improved over the course of the next five minutes, following administration of 50 mg intravenous frusemide (due to the suspicion of pulmonary oedema), 100 mg intravenous hydrocortisone and 10 mg intravenous chlorpheniramine. During this time the patient developed new atrial fibrillation with fast ventricular response. He did not receive adrenaline boluses or an adrenaline infusion at any point and, aside from the coughing, was not difficult to ventilate or oxygenate. He was woken and extubated as soon as the blood pressure had stabilised. Subsequently his atrial fibrillation was cardioverted with intravenous amiodarone. Mast cell tryptase measurements were performed at one hour after the event which showed a rise to 9.0 ng/mL with a subsequent fall to 4.8 ng/mL (both values within normal range).

The patient had no recollection of the event when he was debriefed after recovery from anaesthesia. In accordance with hospital protocols for suspected perioperative anaphylaxis, he was given an information letter detailing the event and suspected culprit drugs, a letter was sent to his General Physician, notes were made in his clinical file, and a referral was made to the local perioperative allergy service.

On subsequent skin prick testing at the perioperative allergy clinic, the patient showed a strongly positive reaction to sugammadex. Intradermal testing was not performed due to the strongly positive skin prick test. Intradermal testing was performed to dexamethasone (negative) and chlorhexidine (due to the possibility of delayed skin absorption) and was also found to be positive. The patient has been counselled to avoid both sugammadex and chlorhexidine although the history and skin prick reaction make sugammadex the most likely culprit in this instance.

Due to historical and licensing factors, the use of sugammadex has been less widespread in UK anaesthetic practice compared to countries such as Japan, Australia, and the United States. Thus, UK reports of anaphylaxis to sugammadex are rare. The first UK case report of sugammadex allergy was published in 2017 [4]. However, in countries where its use is more widespread, studies have demonstrated a relatively high rate of hypersensitivity reactions to the drug [5,6]. A retrospective, single centre study in Japan published in 2018 showed a probable anaphylaxis rate to sugammadex of 0.039%, or 1:2500 administrations (in this centre, sugammadex is the only reversal agent for neuromuscular blockade available as neostigmine was not stocked, and anaphylaxis was defined clinically, not on testing). This was close to the rates quoted for rocuronium or succinylcholine in a study published in 2018 [5]. The same group conducted a retrospective study comparing the incidence of anaphylaxis to sugammadex with that of neostigmine over five years in four hospitals in Japan, this time utilising immunological testing to confirm anaphylaxis. In this paper the authors demonstrated an incidence of anaphylaxis to sugammadex of 1:5000, or a rate of 0.02% [2]. There were no cases of anaphylaxis to neostigmine. It remains unclear whether this high rate is unique to Japan, where sugammadex use is widespread and up to 10% of the population have been exposed to the drug and thereby potentially sensitised to the antigen [5]. Therefore, whether we will see increasing frequency of reactions in countries where its use is currently more restricted, but may increase in the future.

To illustrate, currently 90% of reversed cases in Japan use sugammadex, compared with 9.1% in the UK [2]. When sugammadex comes off patent in 2023 its use in the UK is likely to increase substantially, leading to more adverse events simply as a

statistical fact [6]. Whether or not the markedly elevated Japanese rates of anaphylaxis are as a result of population sensitisation is unclear, particularly when mechanistic studies have failed to show an IgE or even a mast cell degranulation component or to demonstrate increased incidence on subsequent exposures [2,7]. However, concerns around this have led to an editorial suggesting that sugammadex/rocuronium combinations should be reserved for situations where other drugs are contraindicated (e.g.,malignant hyperthermia for succinylcholine) or where they have been shown to have superior clinical outcomes [6].

The established treatment of anaphylaxis is adrenaline, fluids, steroids, and antihistamines. In this case, there was a rapid recovery of the patient in the absence of treatment with adrenaline, which is unusual. This was partially due to slight delay in recognising the problem to arrive at the diagnosis of the clinical situation and an occupation of mental bandwidth with treating the sudden hypotension with fluids and pressor agents that were immediately to hand, coupled with other diagnostic possibilities being raised such as pulmonary oedema. By the time the diagnosis of likely anaphylaxis was made, the patient had recovered sufficiently not to need adrenaline (which we were reluctant to use as the patient had developed fast atrial fibrillation by this stage). Notably, anaphylactic reactions have been reported to sugammadex, rocuronium and the sugammadex/rocuronium complex [8], raising the possibility that the patient had exhibited anaphylaxis only briefly to sugammadex before the drug formed complexes with the remaining rocuronium in his circulation, thereby essentially removing the antigen from his circulation before the full anaphylaxis cascade reaction had been triggered. In effect, this could represent the opposite of the effect observed when rocuronium anaphylaxis is treated with sugammadex to remove the antigen from the circulation. This theory is conjecture only but potentially worthy of further investigation.

Previous studies have demonstrated that sugammadex hypersensitivity reactions are dose dependent, occurring more frequently at higher doses [7,9]. Thus, a reduction in the exposed dose might conceivably mitigate a full-blown anaphylactic reaction. This same study also concluded that the mechanism of hypersensitivity to sugammadex was not necessarily IgE mediated or even a result of direct mast cell degranulation. A second similar study agreed that the mechanism was likely to be non IgE mediated but found no association with dose [10]. None of the subjects in these trials (which studied hypersensitivity reactions to sugammadex administration in awake, healthy individuals) demonstrated rise in their mast cell tryptase levels, despite two of them having confirmed anaphylaxis on skin testing.

It seems clear that the mechanism of sugammadex hypersensitivity and anaphylaxis is poorly understood and that further investigation may be required as the use of sugammadex and therefore, frequency of reactions increases worldwide.

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