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Asystolic cardiac arrest secondary to sugammadex administration in a young patient

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Dear Editor,

Sugammadex is a modified γ-cyclodextrin, used to rapidly and predictably reverse the neuromuscular blocking effects of rocuronium and vecuronium. Its safety profile is generally superior to that of neostigmine [1], however, serious adverse events have been reported. These include profound bradycardia and cardiac arrest [2–8]. Whilst the underlying mechanisms remain unclear the majority of these cases involve older and/or co-morbid patients. We present a case of asystolic cardiac arrest secondary to sugammadex administration in a young, physically healthy patient. Written consent for publication was obtained from the patient.

A 26-year-old female was listed for an elective diagnostic laparoscopy to investigate possible endometriosis. She was an American Society of Anesthesiologists (ASA) physical status II, with a medical history of polycystic ovarian syndrome and depression. She weighed 93 kg with a body mass index of 33 kg m^{-2}. As she had no significant co-morbidities, she did not undergo any formal pre-operative investigations, though a historical electrocardiogram (ECG) from two months prior showed normal sinus rhythm. Her medication history included sertraline 50 mg daily and she had a documented allergy to N-acetyl cysteine, which had previously caused a rash. She had undergone a previous uncomplicated general anaesthesia for a laparoscopic appendicectomy, however, as this had taken place at a distant hospital, the associated notes were unavailable on the day of her surgery.

After applying full monitoring as per the Association of Anaesthetists of Great Britain and Ireland standards the patient underwent intravenous induction of general anaesthesia with fentanyl 1 µg kg^{-1}, propofol 2 mg kg^{-1} and rocuronium 1 mg kg^{-1}. Her trachea was intubated with a cuffed, oral endotracheal tube and anaesthesia was maintained with sevoflurane 2.2% in an oxygen/air mixture. Shortly after induction she received intravenous dexamethasone 6.6 mg, diclofenac 75 mg and morphine 5 mg. The surgical procedure, which lasted 45 minutes, was uncomplicated and she remained haemodynamically stable throughout, with no bradycardia in response to peritoneal carbon dioxide insufflation. Her end-tidal carbon dioxide tension ($EtCO_2$) measured 40.5 mmHg (5.4 kPa) following intubation and rose to a peak of 42.8 mmHg (5.7 kPa) during the surgery. At the end of the operation neuromuscular monitoring revealed a train of four count of zero. Sevoflurane was discontinued and sugammadex 400 mg (~4 mg kg^{-1}) was administered. Reversal of neuromuscular blockade was performed a full 10 minutes after peritoneal desufflation, during which time the patient did not exhibit any haemodynamic derangement. Within one minute of receiving sugammadex however, her heart rate dropped from 68 to 27 beats per minute with the continuous three-lead ECG showing a sinus bradycardia. Non-invasive blood pressure measured 71/38 mmHg, having fallen from 110/62 mmHg. 100% oxygen and intravenous atropine 0.6 mg were immedia-

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tely given followed by a crystalloid fluid flush. The heart rate continued to deteriorate however, rapidly progressing to asystole on the monitor. Cardiac arrest was confirmed by the absence of palpable carotid and femoral pulses and cardiopulmonary resuscitation was commenced. The patient received two minutes of chest compressions and at the first rhythm check there was return of spontaneous circulation (ROSC), prior to the administration of adrenaline.

A post-ROSC arterial blood gas showed a mixed respiratory and minor metabolic acidaemia but was otherwise normal (Table 1). The hypercapnia was likely a result of the arrest given her $EtCO_2$ immediately before her deterioration was normal, measuring 41.3 mmHg (5.5 kPa). After a brief observed period of haemodynamic stability she was uneventfully extubated in theatre. A 12-lead ECG demonstrated normal sinus rhythm. Routine blood tests were all unremarkable (Table 1) and there was no elevation in mast cell tryptase levels, though serum total immunoglobulin E (IgE) was raised. A chest radiograph and transthoracic echocardiogram demonstrated no abnormalities. The patient was admitted to the high dependency unit for close observation before being discharged home after 48 hours with no neurological sequelae.

Due to the elevated total IgE levels skin-prick testing for all the drugs she had been exposed to was performed, including chlorhexidine skin preparation and sugammadex; these were all negative. Subsequent intradermal testing of diluted sugammadex was also negative. It was concluded that the serious adverse reaction was due to the sugammadex itself, rather than an allergy.

This case describes a significant and unexpected clinical deterioration after sugammadex administration, with the temporal association and lack of alternative explanation indicative of a causal relationship. The potential for sugammadex to induce bradycardia and cardiac arrest is acknowledged by the manufacturers [9], though due to rarity of such events, clinicians may be less aware of these risks. In the post-marketing analysis 35 events labelled as cardiac arrest or cardio-respiratory arrest were reported between 2008–2015 [10]. Whilst additional incidents have since been reported, the case mix in the literature is diverse, suggestive of a heterogeneous aetiology to sugammadex-associated cardiac arrest.

Severe hypersensitivity reactions to sugammadex are well documented. This includes reports of cardiac arrests due to both anaphylaxis and type 1 Kounis syndrome (an allergy mediated coronary artery vasospasm) [11–15]. In addition to Kounis syndrome cases of coronary vasospasm without clear allergic involvement have also been described [16, 17]. When considering our patient, it is highly unlikely that her cardiac arrest can be attributed to any of these pathologies. There were no clinical features of anaphylaxis and thorough investigation has refuted a sugammadex allergy. There was equally no evidence of myocardial ischaemia on the antecedent three-lead ECG, the post-arrest 12-lead ECG, or biochemically. Moreover, her cardiac arrest appeared to be secondary to a profound bradycardia, which degenerated into asystole.

The incidence of bradycardia following sugammadex administration is estimated at 1% [10]. The mechanism by which this occurs remains unclear. Sugammadex acts by encapsulating positively charged rocuronium and vecuronium, creating a steep concentration gradient and promoting rapid movement of these drugs away from the neuromuscular junction [18]. As acetylcholinesterase is unaffected it should not exhibit muscarinic actions. Rocuronium, however, has been shown to antagonise the nicotinic acetylcho-

TABLE 1. Point of care and laboratory investigations obtained immediately after return of spontaneous circulation or at the indicated time

Blood test	Result (laboratory reference range)
Arterial pH	7.22 (7.35–7.45)
Arterial pCO_2	8.26 kPa (4.30–6.10 kPa)
Arterial pO_2	27.2 kPa (9.50–13.9 kPa) on FiO_2 – 0.4
Standardised bicarbonate	21.5 mmol L^{-1} (21–26 mmol L^{-1})
Base excess	–3.6 mmol L^{-1} (–2.0–3.0 mmol)
Glucose	6.0 mmol L^{-1} (3.3–6.1 mmol L^{-1})
Lactate	2.0 mmol L^{-1} (0–1.2 mmol L^{-1})
Haemoglobin	133 g L^{-1} (120–150 g L^{-1})
White blood cell count	13.1 x 10^9 L^{-1} (3.9–11.1 x 10^9 L^{-1})
Platelet count	251 x 10^9 L^{-1} (150–410 x 10^9 L^{-1})
Internationalised normalised ratio	1.0 (0.9–1.2)
Sodium	143 mmol L^{-1} (136–145 mmol L^{-1})
Potassium	4 mmol L^{-1} (3.5–5.1 mmol L^{-1})
Magnesium	0.89 mmol L^{-1} (0.66–1.07 mmol L^{-1})
Phosphate	0.97 mmol L^{-1} (0.81–1.45 mmol L^{-1})
Corrected calcium	2.23 mmol L^{-1} (2.15–2.6 mmol L^{-1})
Creatinine	62 μmol L^{-1} (44–80 μmol L^{-1})
Troponin T	< 13 ng L^{-1} (0–14 ng L^{-1})
Total IgE	398 kU L^{-1} (0–81 kU L^{-1})
Mast cell tryptase at time of event	4 μg L^{-1} (2–14 μg L^{-1})
Mast cell tryptase 24 hours post-arrest	4 μg L^{-1} (2–14 μg L^{-1})
Baseline mast cell tryptase taken several months later	3 μg L^{-1} (2–14 μg L^{-1})

pCO_2 – partial pressure of carbon dioxide, pO_2 – partial pressure of oxygen, FiO_2 – fraction of inspired oxygen, IgE – immunoglobulin E

line receptor at the superior cervical ganglia in animal models [19]. It has thus been postulated that its rapid removal by sugammadex may lead to autonomic dysregulation [12], though there is no clinical data to support this theory.

There is some suggestion that sugammadex may alter cardiac conduction based upon published cases of transient second degree (Mobitz type I) and third degree atrioventricular block developing after sugammadex exposure [20–22]. Though this may implicate an element of parasympathetic hyperactivity, it is unlikely to universally explain all episodes of sugammadex-associated bradycardia. In our case asystole evolved from a sinus bradycardia, which did not respond to atropine. Atropine resistance has also been observed by other authors [5, 8, 15] and points away from a purely cholinergic aetiology. It has been proposed that sugammadex may slightly increase the corrected QT interval (QTc) [23, 24], however this has been disproven in safety studies [25, 26]. Additionally, QTc prolongation is more commonly associated with ventricular arrhythmias, such as Torsades de Pointes, rather than profound bradycardia. In our case both the patient's historical and post-arrest ECGs demonstrated a normal QTc.

To our knowledge this is the first case of sugammadex-induced cardiac arrest to involve such a young patient without significant systemic disease. Lohmeiers and Powers [27] reported a similar case in a 26-year-old female, however she would have been categorised as ASA III, due to class III obesity (BMI 46.9 kg m^{-2}). Obesity is a patient factor that has also been reported in several other cases of cardiac arrest caused by sugammadex [4, 5, 15, 28]. This may hold relevance given that sugammadex should be dosed by actual body weight as per the product information [9]. The manufacturers nonetheless claim that the adverse events are not dose-dependent and this seems substantiated by the fact that cardiac arrest occurred after low dose administration (200 mg or less) in all but one of these cases.

This case helps bring to the attention of the anaesthetic community a rare, but life-threatening, adverse event associated with an increasingly commonly used drug. Clinicians should be highly vigilant when administering sugammadex, ensuring that full monitoring is in place, particularly continuous ECG. There should be easy access to emergency drugs, including adrenaline for treatment of bradycardia given the possibility of atropine ineffectiveness. Any progression to cardiac arrest should be managed as per advanced life support algorithms. Though the underlying mechanism is yet to be elucidated, as further cases are published and reported to drug regulatory authorities, there may be scope to identify any patient, anaesthetic or surgical factors that might increase the risk of bradycardia and cardiac arrest amongst patients receiving sugammadex.

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