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Case Report

Secondary Recurarization after Accidental Subcutaneous Application of Rocuronium: Case Report, Review of the Current Literature and Suggestion for Clinical Practice

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Abstract

Sugammadex is frequently used to reverse the neuromuscular blockade achieved by rocuronium and vecuronium in general anaesthesia. The current case presentation describes a patient in whom secondary recurarization occurred after accidental subcutaneous application of rocuronium despite the initially successful reversion with sugammadex. The aim of this case presentation and review of the current literature is to provide troubleshooting and a possible treatment strategy for such scenarios.

Keywords: Recurarization; Rocuronium; Sugammadex; Extravasation; Residual Neuromuscular Blockade

Introduction

Sugammadex is a medication frequently used to reverse the effects of the muscle relaxants rocuronium and vecuronium during anaesthesia. Unlike other reversal agents, sugammadex acts quickly and with high specificity, making it a valuable tool in anaesthesia management. Additionally, it is associated with a reduced risk of postoperative paralysis compared to traditional anticholinergic drugs such as neostigmine [1]. Sugammadex works by selectively encapsulating rocuronium and vecuronium in the plasma, forming a stable and inactive complex that is eventually excreted by the kidneys. The decrease in the plasma concentration of unbound muscle relaxant molecules causes a shift of free muscle relaxants from the effect site (i.e., the neuromuscular junction) back to the plasma, where they are encapsulated by any remaining free sugammadex molecules. Even if 75% of the receptors at the neuromuscular junction are still occupied by muscle relaxants, the remaining 25% are sufficient for normal muscle strength [2]. The term "recurarization" refers to the phenomenon in which a muscle relaxant regains its effect on the neuromuscular junction despite initial muscular recovery. There are several risk factors: redistribution of free muscle relaxants from a peripheral site (e.g., adipose tissue) back into the plasma, coadministration of drugs (magnesium, aminoglycosides) or respiratory acidosis. Recurarization can lead to unwanted effects such as respiratory distress or movement disorders, and requires careful monitoring and potentially re-administration of antagonists. Several case reports have described recurarization despite sugammadex application in children [3,4] and in patients with a pre-existing neuromuscular disease [5-7]. One case describes recurarization in an obese female patient8, which may reflect redistribution of rocuronium from fat tissue back into the plasma [9]. A possible recurarization was also described in a patient after continuous rocuronium infusion for induced hypothermia after cardiac arrest

[10]. Eleveld et al. [11] showed a temporary rebound of muscle relaxation if the applied dose of sugammadex was insufficient (i.e., a short-term reduction in the train-of-four [TOF] ratio). Finally, reoccurrence of respiratory muscle weakness despite sugammadex administration has been described due to a lack of intraoperative neuromuscular monitoring, probably due to insufficient doses of sugammadex if the degree of neuromuscular blockade is not known [12]. In the event of accidental subcutaneous application of relaxants, little is known about drug resorption and how to avoid delayed-onset muscle weakness and the associated risk of respiratory insufficiency and need for re-intubation. The authors herein describe a clinical case in which secondary recurarization occurred after accidental subcutaneous application of rocuronium despite initially successful reversion with sugammadex. The current literature is also reviewed to identify similar cases and provide a clinical practice strategy for such scenarios.

Methods

To identify similar cases or studies, a predefined concept-based search strategy was executed in PubMed. To avoid missing any relevant publications not listed in PubMed, the citations and references of the identified results were also checked. Written informed consent from the patient whose case is presented was obtained. Neuromuscular monitoring was performed using an accelerometric device that measured the motor response of the adductor pollicis after stimulating the ulnar nerve (ToFScan®; Dräger, Lübeck, Germany).

Case Presentation

A 68-year-old patient (172 cm, 86 kg) was admitted to the emergency department of the authors' hospital with evidence of a ruptured abdominal aortic aneurysm (AAA). Known comorbidities included hypertensive cardiomyopathy with normal left ventricular ejection fraction, chronic renal disease (KDIGO stage G3b, baseline creatinine 160 µmol/l, measurement of 181 µmol/l on admission [eGFR CKD EPI 33 ml/min/1.732]) and obstructive sleep apnoea treated with continuous positive airway pressure (CPAP). The patient was immediately transferred to the operating room for emergency open AAA repair. To intubate the patient, a rapid-sequence induction was performed. Initially, sufentanil (40 µg) was administered through a pre-existing intravenous (IV) cannula (20 G) in the patient's left arm. Thiopental (200 mg) and rocuronium (80 mg [0.93 mg/kg]) were then given through a newly inserted peripheral IV catheter in the patient's right arm (17 G). However, the patient remained conscious, suggesting that the IV catheter in the right arm was extravascular. Therefore, thiopental (150 mg) and rocuronium (70 mg [0.81 mg/kg]) were administered, again using the pre-existing peripheral vascular access in the patient's left arm, which eventually led to successful anaesthesia and intubation. Open aortic repair using a Dacron vascular prosthesis was successfully performed, without the need for additional doses of rocuronium. However, the patient experienced profound haemorrhagic shock during the procedure, resulting in a haemoglobin nadir of 43 g/l. Fluid resuscitation consisted of 4 l of crystalloids (Ringer's solution) as well as autologous blood re-transfusion (446 ml) and 2 units of packed red blood cells (total blood loss of 1800 ml). Residual neuromuscular block was measured with a post-tetanic count (PTC) of 5/10. Administration of sugammadex (200 mg [2.3 mg/kg]) resulted in the return of four signals in TOF testing, with a TOF ratio of >90%. The patient survived the procedure and was extubated and transferred to the intensive care unit (ICU). Three hours after the first operation, a second operation was required due to critical ischaemia of the left lower limb. The patient was again transferred to the operating room for embolectomy combined with intra-arterial lysis on the affected limb. Since sugammadex had been administered earlier, succinylcholine (100 mg) was used instead of rocuronium for rapid-sequence induction of general anaesthesia in addition to sufentanil (30 µg) and thiopental (300 mg). No further doses of muscle-relaxing agents were given during the surgery. A total of 2.7 l of Ringer's solution and 1 unit of packed red blood cells were administered. Intraoperative neuromuscular monitoring revealed a fading phenomenon in TOF testing (TOF ratio of 60% with repetitive measurements on both arms), which is typically associated with nondepolarizing muscle relaxants but not with a single dose of succinylcholine. Furthermore, an ongoing drug effect of succinylcholine was unlikely (TOF measurement 30 min after succinylcholine application). Hence, a delayed onset of action of the initially administered rocuronium, which had initially been injected into the extravascular peripheral catheter in the patient's right arm, was suspected. After a new dose of sugammadex (200 mg), the neuromuscular blockade was antagonized, resulting in an instantaneous TOF ratio of 100%, and the patient was extubated. The patient was then transferred back to the ICU for close postoperative monitoring. Spontaneous breathing was preserved. However, more than 24 h later, respiratory failure requiring mechanical ventilatory support occurred, which was attributed to systemic inflammatory response syndrome. The patient's kidney function also declined, eventually leading to the need for renal replacement therapy. During the hospital stay, several subsequent operations and revisions under general anaesthesia were needed because of an ischaemic left colon (due to the intraoperative haemorrhagic shock). Inductions with rocuronium were then tolerated without adverse events.

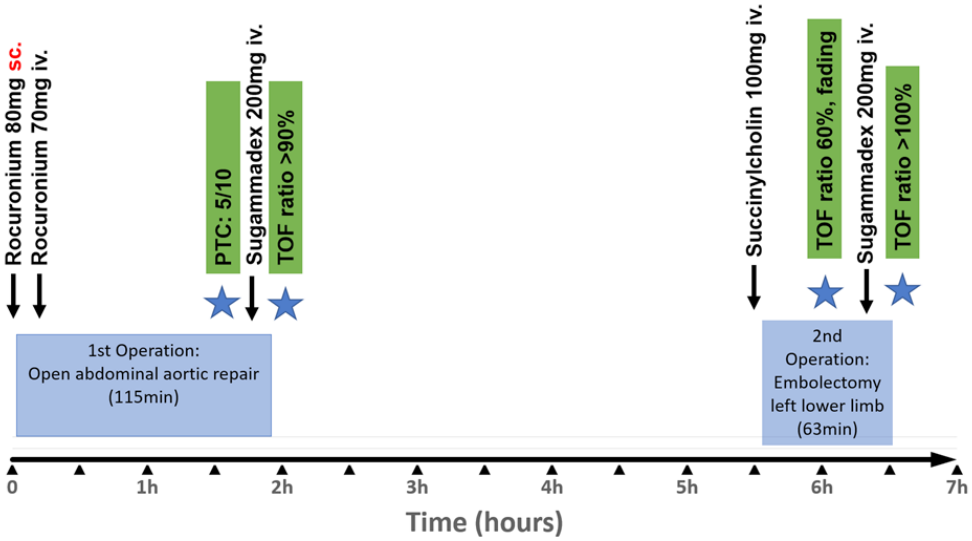

Figure 1: Timeline and dosing of neuromuscular relaxants (PTC: post-tetanic count, TOF: train of four, sc.: subcutaneous, iv: intravenous).

Discussion

The current case highlights the occurrence of a second onset of rocuronium action despite initial reversal with sugammadex. This second onset was probably due to ongoing absorption of rocuronium from the subcutaneous depot into the plasma, which either exceeded the binding capacity of sugammadex or occurred when no more sugammadex was present in the plasma. Additionally, the haemorrhagic shock with altered organ perfusion may have led to reduced hepatorenal clearance of rocuronium, creating a mismatch between subcutaneous absorption and elimination. There have been a few case reports documenting unpredictable resorption following accidental subcutaneous injection of rocuronium. Takagi et al. [13] measured plasma concentrations of rocuronium in four patients who received accidental subcutaneous injections. Although these patients had similar recovery times to those with IV administration of rocuronium after reversal with sugammadex, there were notable prolongations of elevated plasma levels without reversal. This was particularly true in an elderly patient with arteriosclerosis (997 min until full recovery) compared to a younger patient (391 min until full recovery). This suggests a potential role of delayed subcutaneous resorption in elderly patients with cardiovascular compromise, as was the case in the current patient in haemorrhagic shock. In the present case, there was still a fading in the TOF measurement 6 h after initial rocuronium administration before a second dose of sugammadex was administered. Kim et al. [14] reported on a safe discharge to the ward after a 4-h monitoring period following extravasation of 0.6 mg/kg rocuronium with a TOF count of 4 in a 38-year-old obese female patient (BMI 32.9 kg/m2) during left mastectomy with administration of 2 mg/kg sugammadex. Similarly, in a recent publication [15], a 59-year-old obese woman weighing 120 kg with a BMI of 48.1 kg/m2 received 50 mg of rocuronium accidentally subcutaneously during laparoscopic cholecystectomy. The rocuronium had no initial effect, so an additional 50 mg was administered intravenously. At the end of the procedure, the patient had 2/4 TOF twitches and 2 mg/kg of sugammadex was administered, resulting in complete and sustained recovery from the neuromuscular blockade. The patient was then discharged home after a 4-h monitoring period. Doshu-Kajiura [16] and colleagues documented a safe reversal with sugammadex in a patient with chronic renal failure who had accidentally received subcutaneous injection of rocuronium. In this case, the TOF count was 2/4 twitches, but due to the uncertainty of whether the TOF count was falling or rising, the authors decided to administer a relatively high dose of 4.5 mg/kg sugammadex. Navare and colleagues [17] reported a sustained and successful reversion of the neuromuscular blockade with 4 mg/kg sugammadex in a dialysis patient with a subcutaneous depot of rocuronium and a TOF of 1/4 twitches, arguing that the reduced renal clearance of sugammadex in this patient population favours encapsulating the slowly resorbed rocuronium molecules from the subcutaneous tissue. In contrast to all previously mentioned case reports, a second neuromuscular blockade was measurable several hours later in the present case, despite initially successful neuromuscular recovery with the use of sugammadex. It is important to note that unlike the other mentioned cases, the initial dose of sugammadex was lower than the manufacturer's recommendations [18] (4 mg/kg in deep blockade defined as 1–2 PTCs, TOF count 0) in the current case. Nevertheless, since relaxometry showed evidence of reversion of the rocuronium molecules at the neuromuscular junction at that

time, no additional dose was given in the first instance. However, "high-risk" patients like the current patient may experience unpredictable subcutaneous absorption of rocuronium, leading to a second onset of muscle weakness later on. A possible strategy could be to split the sugammadex dose over time. Therefore, the suggested approach for managing accidental extravasation of rocuronium involves several steps. First, an attempt to aspirate the injected fluid from the extravascular IV line. Second, administration of a first sugammadex dose to antagonize the actively acting rocuronium depending on the degree of neuromuscular blockade as per the manufacturer's recommendations (2 mg/kg in moderate neuromuscular block, 4 mg/kg in deep block [18]). Third, calculation of the amount of sugammadex required to encapsulate the administered subcutaneous rocuronium and splitting of this dose over time. To determine the necessary dose, the molecular weights of sugammadex and rocuronium can be used: sugammadex has a molecular weight of 2002.2 Dalton [19], rocuronium of 529.8 Dalton [20]. Since one molecule of sugammadex encapsulates one molecule of rocuronium [21-23] a dose of 3.78 mg sugammadex is needed for every 1 mg of rocuronium. For reasons of safety and simplicity, using a 4:1 ratio (4 mg of sugammadex for every 1 mg of rocuronium) is suggested. After determining the appropriate (second) dose of sugammadex, this can be administered in fractions over time until the calculated total dose is achieved. The authors recommend administering 50–100 mg sugammadex, every 1–2 h until the total dose is achieved. This approach ultimately leads to encapsulation of all administered rocuronium molecules and takes into account the continuous subcutaneous resorption of rocuronium. Taking the current case as an example, since there was still a deep neuromuscular block present at the end of the first operation (PTC of 5), 4 mg/kg sugammadex should have been injected first to reverse the active mainly intravenously administered rocuronium (4 x 86 kg = 344 mg). Next, the dose of sugammadex expected to encapsulate the subcutaneous depot of rocuronium (80 mg) would have been 320 mg (4 x 80mg). Splitting this into fractions of 80 mg per hour (four applications in total) could have minimized the risk of residual muscle weakness several hours later. It is important to note that the time intervals and fractioned doses of sugammadex application suggested herein are solely empirical. A TOF ratio of 60% was measured 4 h after the first sugammadex application in the present case, suggesting that recurarization may occur in a matter of hours, not days. However, it is uncertain whether the TOF ratio was falling or rising at that time. Therefore, it remains crucial to closely observe such patients in a monitoring unit.

Conclusion

In the event of accidental subcutaneous injection of rocuronium, ensuring an appropriate dose of sugammadex is crucial to prevent secondary recurarization. Additionally, close postoperative monitoring of the patient is essential, given that the pharmacokinetics of a subcutaneous rocuronium depot can become unpredictable. After initial antagonization of the active rocuronium, fractionated administration of sugammadex over time may help to encapsulate all remaining rocuronium molecules and address the continuous resorption of the drug.

Disclosure

Author Contributions: Conceptualization, Y.W. and F.M.; methodology, Y.W. and F.M..; validation, F.M. and I.B.; investigation, Y.W. and F.M.; resources, I.B. and F.M..; data curation, Y.W..; writing original draft preparation, Y.W.; writing review and editing, F.M..; visualization, Y.W.; supervision, F.M.; project administration, Y.W.; All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: Anonymized data supporting the study results can be provided followed by request sent to the corresponding author's e-mail.

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