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Case Report

Intraoperative Severe Anaphylactic Shock to Sugammadex in an Anesthesia-Naive Patient

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Abstract

Sugammadex is a revolutionary drug for the reversal of neuromuscular blocking agents. It is a modified gamma cyclodextrin that directly binds and inactivates steroidal nondepolarizing neuromuscular blockers to facilitate reversal with fewer adverse effects than previously used reversal agents. In general, literature supports its favorable safety profile with common side effects being nausea, vomiting, headache, dry mouth and dizziness. Sugammadex can cause hypotension and bradycardia, with rare reports of sugammadex anaphylaxis at estimated incidence rates between 0.01-0.039%. The present case describes the clinical presentation and management of severe anaphylactic shock following sugammadex administration intraoperatively to an anesthesia-naïve patient.

Key Words: case report; anaphylaxis; sugammadex; shock

Introduction

Neuromuscular blocking agents (NMBAs) have been used in anesthesiology practice for much of the last century [1]. These drugs are widely employed in general anesthetics to optimize intubating conditions and improve surgical exposure. NMBAs are generally categorized as either depolarizing or nondepolarizing according to their mechanism of action, with the use of non-depolarizing agents more common in current clinical practice [1].

Reversal of nondepolarizing NMBAs is necessary prior to emergence and extubation to promote the recovery of respiratory and laryngeal motor function. Prior to FDA approval of sugammadex in 2015, cholinesterase inhibitors (e.g. neostigmine) were the only reversal agents available for non-depolarizing NMBAs. Cholinesterase inhibitors function in an indirect manner to increase the concentration of acetylcholine at the neuromuscular junction to competitively antagonize the effect of non-depolarizing NMBAs on postsynaptic receptors. However, sugammadex is a new reversal agent with a novel mechanism; this modified gamma cyclodextrin directly encapsulates steroidal non-depolarizing NMBAs, immediately terminating their effect [2]. Compared to cholinesterase inhibitors, sugammadex has several important favorable aspects to support its current usage, including but not limited to: faster and more predictable reversal of moderate neuromuscular blockade (indicated by lower variability in recovery times) [3], faster reversal of deep paralysis (including after rapid-sequence induction doses) [4], and significantly reduced incidence of residual neuromuscular blockade [5]. Additionally, in some scenarios, sugammadex can be a critical component to navigating out of a "cannot intubate, cannot ventilate" situation. Finally, some studies show that reversal with sugammadex is linked to a lower incidence of postoperative pulmonary complications [6], although the data is currently conflicting with others showing no difference [7,8].

Sugammadex is generally considered to be safe with a limited side effect profile. It has been shown to have a lower risk of bradycardia (RR 0.16) and postoperative nausea/vomiting (RR 0.52) compared to neostigmine [9]. In the 2015 FDA approval dataset, sugammadex was associated with hypotension (5%), vomiting (12%), bradycardia (1%), headache (5%) and nausea (26%) [10, 11]. Anaphylaxis is the most rare, but life-threatening, reaction to sugammadex with an incidence estimated at 0.01-0.039% [12].

We report here a case of severe intraoperative anaphylactic shock after routine administration of sugammadex to reverse a non-depolarizing NMBA following elective inguinal hernia repair. A signed Health Insurance Portability and Accountability Act authorization to use and disclose existing information was obtained from the patient. This case report adheres to CARE guidelines and did not require institutional review board approval.

Case Presentation

A 38 y.o. male weighing 74kg (BMI 29kg/m2) with a medical history of type 2 diabetes mellitus (hemoglobin A1c 7.9%) presented for elective inguinal

hernia repair. His preoperative anesthetic evaluation was otherwise unremarkable. The patient specifically denied prior anesthetic exposure and had no family history of anesthetic problems.

Intraoperatively, the patient underwent an uneventful and hemodynamically stable induction with lidocaine, propofol and 50mg of rocuronium. He was maintained on sevoflurane (average expired concentration of 2.0% throughout the case). Throughout the two-hour case, rocuronium was re-dosed twice totaling an additional 50mg. Mean arterial pressure (MAP) averaged 75mmHg, with no pressor requirement. Pulse oximetry (SpO2) ranged from 98-100% on 50% inspired oxygen. Heart rate ranged from 60-120bpm with no EKG abnormalities.

Within three minutes of sugammadex administration, the patient developed sustained severe hypoxia with SpO2 in the 70's (nadir 74%), increased airway pressures (37 from 14), and hypotension with MAPs in the 40's (nadir 42mmHg) refractory to increased fresh gas flows, 100% FiO2, alveolar recruitment, pressure-driven intravenous crystalloid boluses (total 2L), and high dose vasopressors (2000mcg phenylephrine, 150mg ephedrine, norepinephrine at 20µg/min). Additional large-bore peripheral intravenous access and invasive arterial pressure monitoring were rapidly established. A focused ultrasound examination was performed to assess for lung and cardiac function, which was within normal limits aside from an under-filled heart. ST elevations, urticaria, and angioedema were then seen and the diagnosis was narrowed to suspected sugammadex-induced anaphylaxis. Immediate improvement in hemodynamics, other vital signs, and airway pressures were noted after a 100µg epinephrine bolus and initiation of a 2µg/min infusion. The patient concurrently received hydrocortisone, famotidine, and diphenhydramine [13]. Figure 1 provides the time course of intraoperative events during the anaphylactic period.

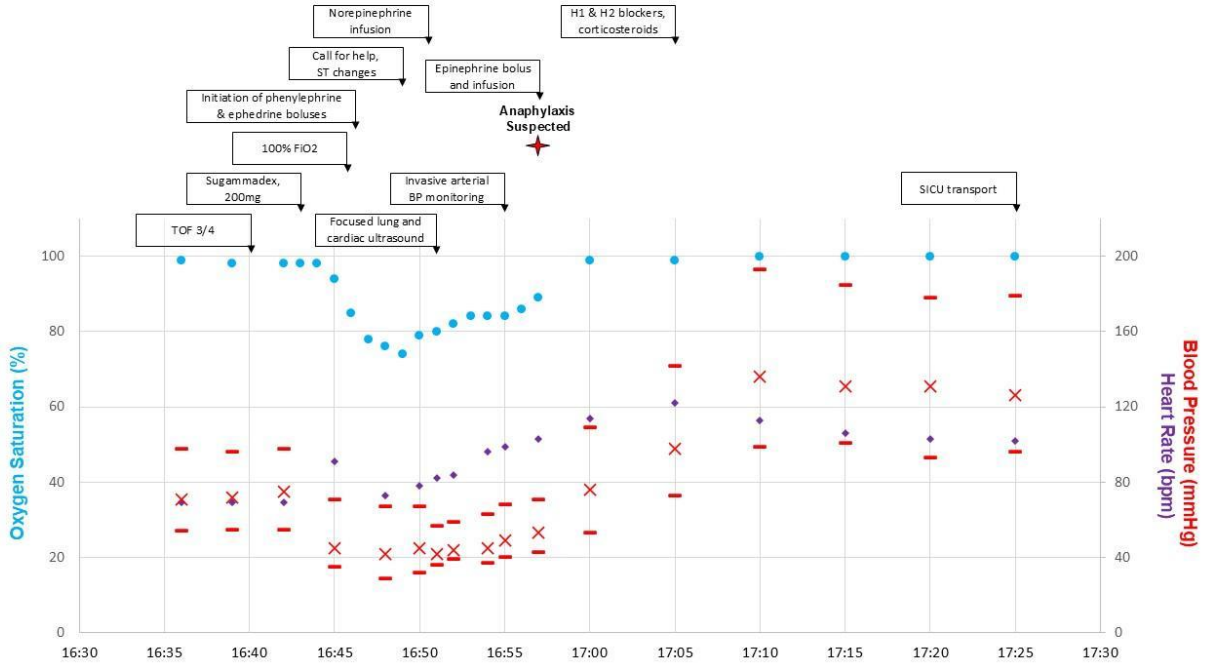

Figure 1: Time course of intraoperative events surrounding sugammadex anaphylactic period: X Axis - Intraoperative Time (in minutes); Y Axis - Scale ranging from 0 to 100; Red X - Mean Arterial Pressure (mmHg); Upper Red Line - Systolic Blood Pressure (mmHg); Lower Red Line - Diastolic Blood Pressure (mmHg); Purple Dot - Heart Rate (BPM); Blue Dot - Oxygen Saturation (% out of 100)

After the patient was stabilized intra-operatively, he was transferred to the surgical intensive care unit (SICU) intubated and sedated with propofol and continued low-dose epinephrine infusion at 1µg/min due to severe angioedema preventing extubation. Post-operative care in the SICU included scheduled intravenous dexamethasone, crystalloid fluid resuscitation (3L), and epinephrine infusion (initially continued at 1µg/min and turned off on postoperative day (POD) #1). The patient was extubated at approximately 17h and discharged on POD #2.

Supporting the diagnosis of severe anaphylactic shock, laboratory values were notable for a peak lactate of 4.01mmol/L (normal 0.5-2.2mmol/L) and tryptase of 83.8ng/mL (normal 1-15ng/ml) at 23min and 75min, respectively, after sugammadex administration. Lactate levels resolved (1.29) prior to discharge. Tryptase down-trended to 4.0 at 216min and <1ng/ml at approximately 15h.

Discussion

This report describes the clinical presentation and management of confirmed severe anaphylactic shock following administration of sugammadex in an ASA 2 anesthesia-naïve patient undergoing an elective inguinal hernia repair at a large academic institution. We describe the initial presentation of intraoperative undifferentiated shock, with subsequent narrowing of the differential to anaphylactic shock.

Perioperative anaphylaxis is uncommon but often results in significant patient morbidity and mortality. The overall rate of perioperative anaphylaxis is reported at approximately 1 in 10,000 [14], with a rate of fatal or near fatal anaphylaxis events of 1.26 in 100,000 procedures [15]. In 90% of cases, NMBAs, antibiotics, latex, chlorhexidine, and blue dye are identified as the inciting agents [12]. Accordingly, most cases of intraoperative anaphylaxis occur towards the beginning of an anesthetic. Anaphylaxis to sugammadex is quite rare (0.01% to 0.039%) in clinical practice and occurs at the end of an anesthetic when hemodynamics and vital signs are naturally rapidly fluctuating, a combination that often results in a significant delay in diagnosis [12]. Furthermore, no risk factors for sugammadex anaphylaxis have been identified, making it very difficult to predict [12]. Indeed, in this case, while the diagnosis of sugammadex anaphylaxis was made without significant delay, it was not immediately suspected for these reasons.

Sugammadex anaphylaxis may occur without prior sugammadex exposure which can lead to delays in diagnosis [12,16]. In two prior case studies, 5 out of 6 cases of anaphylaxis had no previous exposure to sugammadex [17,18]. Sugammadex is a modified gamma cyclodextrin, and cyclodextrins are used as food preservatives, drug carriers, and in commercial products so exposure to or ingestion of these may lead to sensitization [12,16].

A systematic review by Arslan et al. demonstrated that hypotension and hypoxia were present in 93.9% and 45.4% cases of sugammadex anaphylaxis, respectively [19]. A systematic review by Zecic et al. demonstrated symptoms of hypotension (92%), erythema (76%), desaturation (40%), swelling/edema (28%) and wheezing (28%) as most common [20]. Finally, a retrospective review of general perioperative anaphylaxis demonstrated signs of hypotension (46%), bronchospasm (18%), tachycardia (9.8%), oxygen desaturation (4.7%), and bradycardia (3%) [14].

The diagnosis of sugammadex anaphylaxis was made here based on the acute presentation within minutes following sugammadex administration with simultaneous involvement of the skin (e.g. urticaria) and mucosal tissue (e.g. angioedema) following initial respiratory compromise and hypotension, in accordance with the World Allergy Organization guidelines [21]. Notably, no other drugs had been administered within a reasonable timeframe to have served as the anaphylaxis inciting agent. Additionally, a tryptase level was drawn at 75min and was significantly elevated at 83.8ng/ml. This degree of elevation combined with a normalized tryptase level at 15h strongly support the diagnosis of anaphylaxis. Finally, this patient had evidence of anaphylactic shock, with an elevated lactate of 4.01 at 23min after sugammadex administration.

Conclusion

Intraoperative sugammadex anaphylaxis is a very rare, but life-threatening event. While the acute, severe instability posed challenges here, the quick resolution and favorable recovery of this patient demonstrates the importance of swiftly diagnosing and treating intraoperative sugammadex anaphylaxis. The diagnosis however poses quite a challenge to the clinician, especially since it tends to occur at the end of an anesthetic which is uncommon for intraoperative anaphylaxis, happens during a time of expected rapidly fluctuating hemodynamics, and can occur without prior sugammadex exposure. This triad further increases the potential for patient morbidity and mortality, and highlights the need for anesthesiologists to remain vigilant for signs of anaphylaxis after administration of sugammadex, possibly even more so in sugammadex naive patients, and especially since sugammadex administration will be more frequent as it comes off patent [12]. This report may serve as a reminder to consider sugammadex anaphylaxis when undifferentiated shock is encountered in the emergence or postoperative phases of care.

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Alisa Wilkinson, MD: This author helped care for the patient, review the literature, and draft the manuscript.

Ziyad O. Knio, MD: This author helped care for the patient, review the literature, and draft the manuscript.

Alexander Metzger, MD: This author helped care for the patient, review the literature, and draft the manuscript.

Nabil Elkassabany, MD: This author helped care for the patient, and revise the manuscript.

Jenna L. Leclerc, MD, PhD: This author helped care for the patient, review the literature, and revise the manuscript.

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