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Case Report

Role of Sugammadex, Significance of its Dose and Timing for Rocuronium Induced Medically Refractory Anaphylactic Shock: A Case Report

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Abstract

Rocuronium-induced anaphylaxis (RIA) during the perioperative period is a rare life-threatening event. Despite, the available evidence of sugammadex for RIA, there has been no standardized approach for the management of this critical scenario. Therefore, we propose a systematic approach for diagnosing and treating RIA. We, also present a case report of a medically refractory anaphylactic shock from rocuronium, which was effectively treated with sugammadex. Our literature review and experience suggest that sugammadex can be an effective treatment option for medically refractory rocuronium-induced anaphylaxis, and thus should be part of the armamentarium for RIA.

Keywords: Sugammadex, Rocuronium, Life-threatening anaphylaxis, Perioperative anaphylaxis, Rocuronium-induced anaphylaxis, Sugammadex dosing and timing.

Introduction

Anaphylaxis in the perioperative period, especially during general anaesthesia is rare, but potentially life threatening event. The incidence of perioperative anaphylaxis varies from 1:3,500 to 1:20,000 cases [1]. The most common contributory agent for perioperative anaphylaxis is neuromuscular-blocking agents [2]. In addition, among these, rocuronium and succinylcholine have the highest incidence of perioperative anaphylaxis.

The diagnosis and treatment of Rocuronium Induced Anaphylaxis (RIA), during general anesthesia, can be challenging, due to multiple medications being administered at the same time during induction and, general anaesthesia masking many symptoms of anaphylaxis, such as pruritis, wheezing, and difficulty in breathing. This can potentially cause a significant delay in the recognition and treatment of anaphylaxis.

In all cases of anaphylaxis, the first line of management should be the removal or termination of exposure to the offending agent, which poses a challenge after intravenous administration of the culprit drug. The first-line medical management for anaphylaxis is adequate oxygenation, epinephrine, fluid resuscitation, and hemodynamic support. The second-line management includes intravenous steroids and antihistamines.

Sugammadex is a modified gamma-cyclodextrin that irreversibly binds rocuronium molecules. Since the advent of sugammadex, as a reversal agent for rocuronium, there are several case reports on the utility of sugammadex for RIA [3, 4]. In the case of RIA, sugammadex attenuates the immunological cascade by binding to rocuronium [5] and encasing the entire molecule. Despite, the available evidence of sugammadex for RIA, there has been no standardized protocol or systematic approach for the management of this critical scenario.

Therefore, we propose a systematic approach for diagnosing and treating RIA. The authors also present a case report of medically refractory anaphylactic shock from rocuronium, which

was effectively and expeditiously treated with sugammadex. Informed consent for the publication of this case report was obtained from the patient.

Case Description

A 42-year-old male, weighing 93 kg, with no known drug allergies was scheduled to undergo an elective microsurgical testicular sperm extraction surgery for infertility. His past medical history was significant for childhood leukemia treated with chemotherapy. The patient was otherwise fit and well. The Recent laboratory workup was within normal limits. On examination, the patient's airway and his preoperative vitals were normal.

On arrival at the operating room, the patient was connected to standard monitors in accordance with ASA guidelines. Pre-induction verification was conducted prior to preoxygenation. Induction agents included 2 mg of intravenous midazolam followed by 50 micrograms of fentanyl, 100 milligrams of lidocaine, 250 milligrams of propofol, and 60 milligrams of rocuronium. The patient was intubated successfully with a size 8.0 oral endotracheal tube. The patient was maintained on 0.6 Fio2 and 2% sevoflurane to achieve a MAC of 1.2. It was noted that after a mere 8 minutes from the induction, the patient became severely hypotensive with a blood pressure of 60/30 mmHg and tachycardic to a heart rate of 120 beats per minute. Immediately the patient was placed on 100% Oxygen and the hypotension was treated with phenylephrine 400 micrograms aliquots and rapidly infusing intravenous fluids.

Despite these efforts, the patient continued to show signs of circulatory collapse. Working with the anaphylaxis algorithm, epinephrine boluses were titrated to maintain normal blood pressure, intravenous diphenhydramine 50 milligrams, and hydrocortisone 100 milligrams were immediately administered. Since the patient had received rocuronium as part of the induction and no antibiotics were administered thus far, the authors suspected RIA. Resuscitation with epinephrine boluses and fluid administration was continued. Ultrasound-guided right radial and right internal jugular venous cannulation was secured for ongoing hemodynamic management. A complete blood count, basic metabolic panel, arterial blood gases, and serum tryptase levels were requested.

Due to the persistent refractory hemodynamic instability and the suspicion of RIA, a clinical decision was made to administer sugammadex to mitigate the effects of the suspected offending agent rocuronium. The patient received 16 mg/kg of sugammadex, a total dose of 1488 milligrams. At this stage, an epinephrine infusion was also commenced. After 15-20 minutes of sugammadex administration patient's blood pressure started to improve and the epinephrine infusion was eventually discontinued within an hour of initiation Figure: 1 & Figure: 2. After stabilization, the patient was transferred to the medical ICU intubated, for further management. Within a duration of 4 hours, the patient was extubated and no longer required vasopressors. Serum tryptase levels are drawn 30 minutes after the initial hypotensive episode resulting in 13 mcg/l (normal limit: < 11 mcg/l). The patient was discharged after 24 hours of monitoring, with instructions to follow up with the immunology-allergy department for intradermal skin testing in 4-6 weeks.

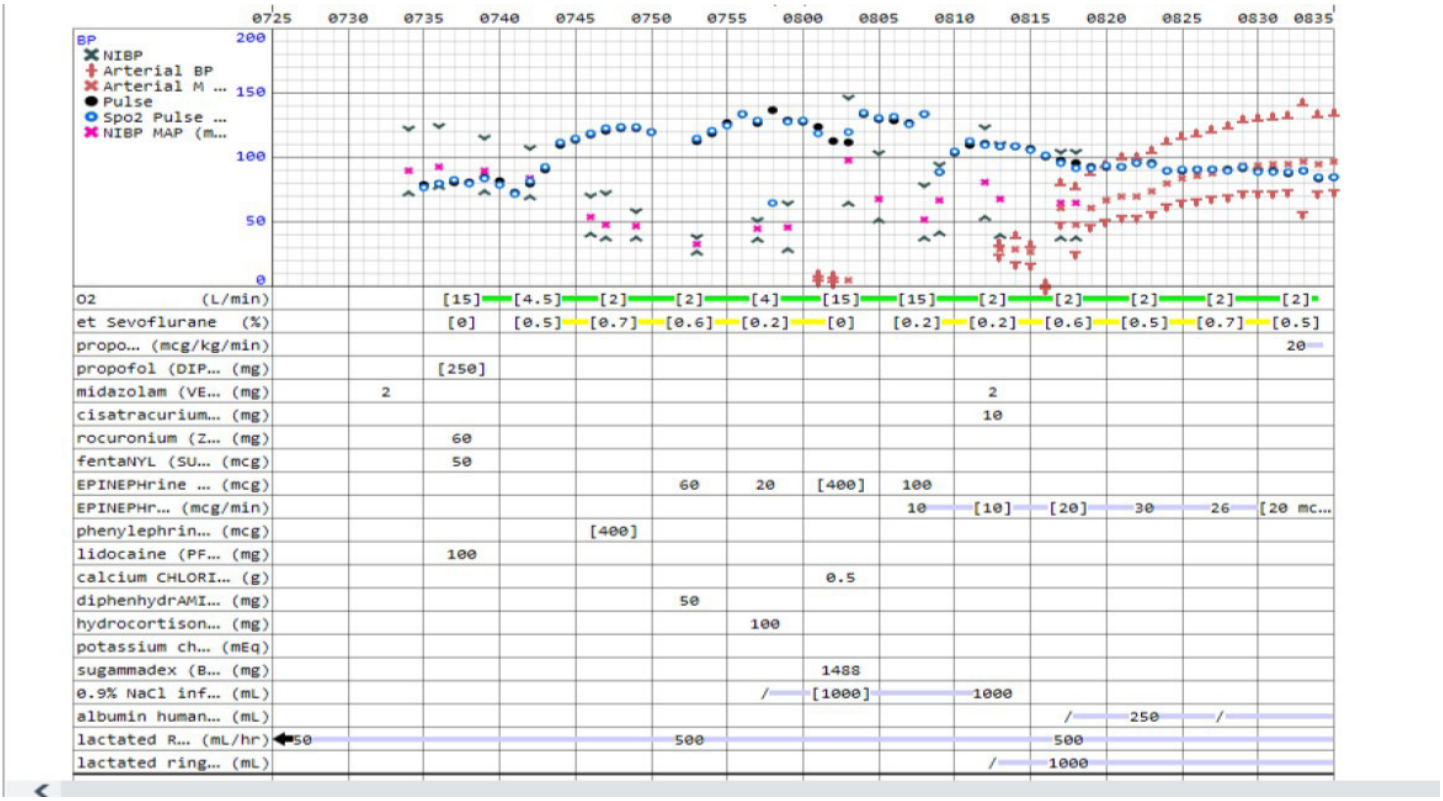

Figure 1: Timeline of sugammadex administration to hemodynamic stability indicated by the red and green arrows respectively. Within 20 minutes of sugammadex administration, we were able to wean the epinephrine infusion steadily which is marked by a blue arrow.

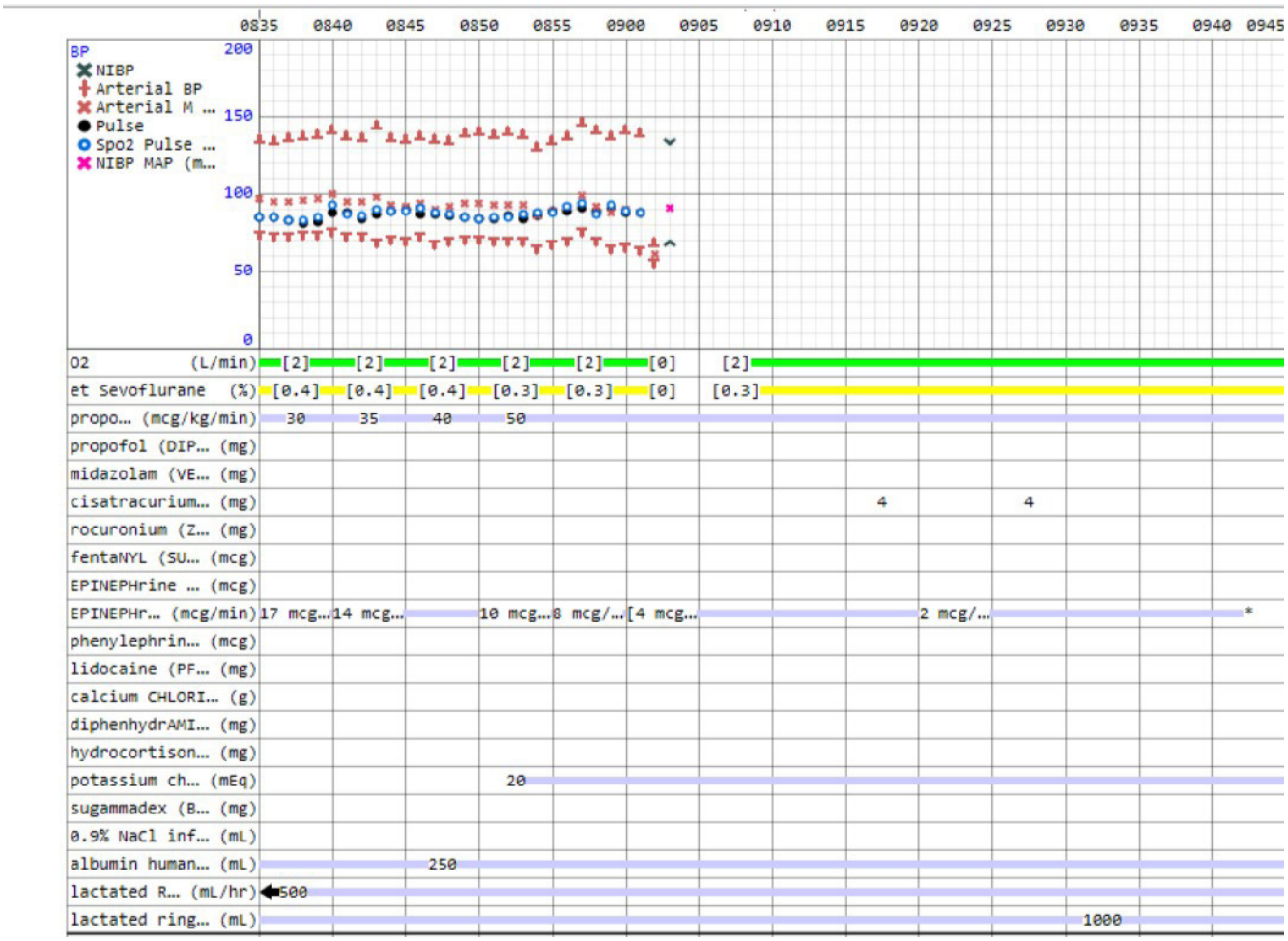

Figure 2: Timeline of clinical response to epinephrine infusion. Within 1 hour of sugammadex administration, epinephrine infusion was weaned off to a minimal dose.

Six weeks following discharge, the intradermal skin testing was performed with midazolam, lidocaine, fentanyl, propofol, and rocuronium at different encounters. The author's suspicion of RIA was confirmed with a positive intradermal test result for rocuronium alone. The patient had a wheal of 3 mm greater than negative control in the skin prick/intradermal test to rocuronium. Intradermal testing was negative for all the other medications. In conclusion, it was confirmed that the patient had a severe allergy/anaphylaxis to rocuronium.

Discussion

In our case, the diagnosis of rocuronium-induced anaphylaxis was made since the patient received only moderate doses of propofol and fentanyl, which is an otherwise young, healthy male, is unlikely to cause this degree of hemodynamic embarrassment. In addition, amongst the agents administered before the anaphylactic shock, rocuronium is known to have the highest potential to cause anaphylaxis. Since the patient did not receive any antibiotics during the induction period, they were not considered to be contributory to the clinical picture.

The possible differential diagnosis at that time included acute coronary syndrome (ACS), pulmonary embolism, and tension pneumothorax from a ruptured bulla. The patient did not exhibit any acute ST-segment EKG changes and given his healthy preoperative cardiac status; ACS was unlikely to be the cause. Given his stable respiratory parameters and adequate gas exchange, we considered pulmonary embolism and tension pneumothorax to be less likely. Hence, our diagnosis was an anaphylactic shock, most probably from RIA.

The mechanism of RIA occurs through IgE/Fcε receptor-mediated activation of mast cells and basophils. Immediately

after the diagnosis, our management included first-line agents, epinephrine, and fluid resuscitation. Steroids and antihistamines were also administered. Due to the medically refractory hypotension despite administration of vasopressors and fluids, a clinical decision was made to administer sugammadex to mitigate the effects of rocuronium IgE mediated reaction. Serial laboratory draws of serum histamine and tryptase can aid in the retrospective diagnosis of anaphylaxis [6]. After administration of sugammadex, there was an improvement in the hemodynamics, and the patient was subsequently weaned off epinephrine.

Along with several theories that support the use of sugammadex for rocuronium-induced anaphylaxis, we confidently postulate that sugammadex antagonizes the antigenicity of rocuronium by encasing the molecule completely; although a few in-vivo studies have shown that, the antigenic portion of rocuronium is still exposed projecting out of the encapsulated rocuronium-sugammadex complex [7], the significance of which is not clearly elucidated.

The author's rationale for the utilization of sugammadex was, although it cannot inhibit the mast cell degranulation and inflammatory mediator release that previously befell, it does potentially reduce the propagation of the inflammatory cascade, which helps in decreasing the intensity of the reaction and rendering the scenario more amenable to treatment with epinephrine and steroids. Since sugammadex encapsulation of rocuronium is believed to decrease the intensity of the cascade, the dosing and timing of sugammadex administration are also crucial and there are no current recommendations or guidelines surrounding this. In accordance with some case reports that recommend 16mg/kg of sugammadex [8], the authors strongly believe that a full reversal dose of sugammadex, which is 16 mg/kg, must be administered, for sugammadex to encase all the free circulating rocuronium molecules. The timing of administration should also be early to prevent escalation of the inflammatory cascade.

Of note, sugammadex itself can cause anaphylaxis [9]. Therefore, it is important to use sugammadex only when the suspicion of rocuronium-induced anaphylaxis is high and if the manifestations are refractory to the conventional therapy.

In conclusion, the authors were able to successfully treat a case of RIA shock, which was refractory to first-line and second-line agents with a full reversal dose of sugammadex. Our literature review and experience suggest that sugammadex can be an effective treatment option for medically refractory rocuronium-induced anaphylaxis [10]. The authors put forward a systematic approach for the management of RIA Figure 3.

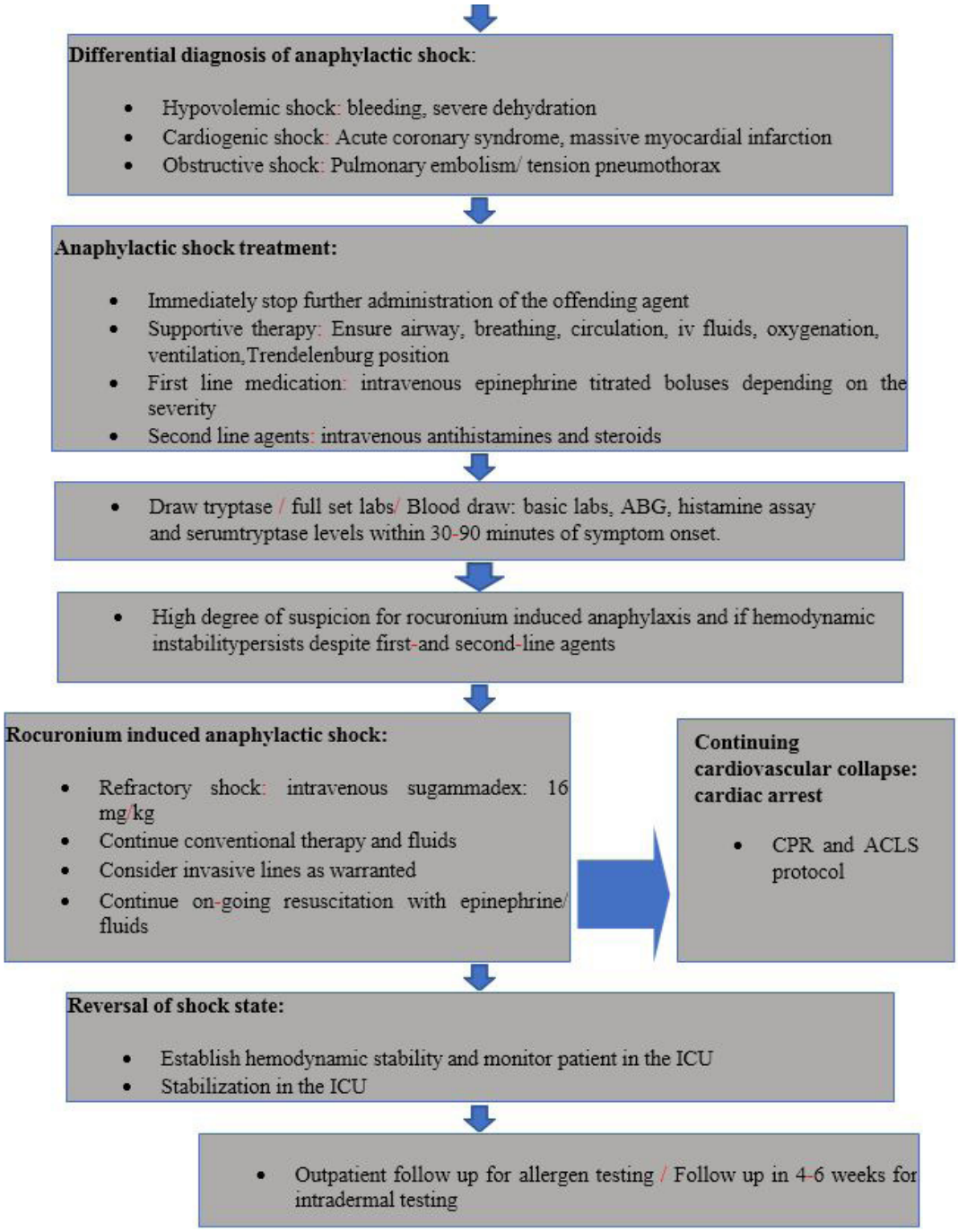

Figure 3: Systematic approach for the management of rocuronium induced anaphylaxis.

However, further research is warranted to validate this off-label use of the drug, patient selection, the optimal dosing, and the timing of administration of sugammadex for rocuronium-induced anaphylaxis. The life-threatening nature of the anaphylactic shock and the role of sugammadex in the management of anaphylactic shock based on several case reports clearly outweigh the few theoretical extrapolations that suggest that sugammadex may not be effective in treating the anaphylactic shock. The authors firmly believe that sugammadex should be a part of the armamentarium for managing RIA-until proven otherwise. Finally, the authors recommend the diagnosis of anaphylaxis should be established after a prospective intradermal skin test 4-6 weeks after the initial insult.

Author's Contribution

Santhalakshmi Angappan: Primary author, case report write-up, and literature review.

Mohamed Fayed: This author helped with the literature search and write-up.

Amna Shaikh: This author helped with the literature review.

Ravnita Sharma: This author came up with the suggestion to write up a case report and helped proofread the write-up.

Nandak Choksi: This author was a mentor and extended help with proofreading the write-up.

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