



Case Report

A case of anaphylaxis apparently induced by sugammadex and rocuronium in successive surgeries[☆]



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Received 31 October 2014; accepted 12 November 2015

Keywords:

Anaphylaxis;
Rocuronium;
Sugammadex

Abstract Rocuronium is the agent most frequently involved in perioperative anaphylaxis, and sugammadex has also been known to induce anaphylactic reactions. We describe a case of successive anaphylactic episodes that seemed to be induced by clinical doses of rocuronium and sugammadex. The patient was a 19-year-old woman who had a medical history of asthma, but no history of surgery. She had been injured in a fall, and several surgeries were scheduled for multiple bone fractures. At the first surgery under general anesthesia, she developed anaphylaxis 5 min after sugammadex administration. A second general anesthesia for treatment of calcaneal fracture was induced uneventfully without neuromuscular blockade after 10 days. A third general anesthesia was scheduled to reinforce the spinal column 12 days after the first surgery. She developed anaphylaxis 8 min after rocuronium administration. The level of plasma histamine was elevated, but serum tryptase level remained normal. This surgery was canceled and rescheduled without use of a neuromuscular blockade. Skin tests were performed in a later investigation. The patient showed positive results on intradermal tests for sugammadex and rocuronium, supporting a diagnosis of allergic reactions to both drugs. Clinicians must be aware that anaphylactic reactions can be induced by both sugammadex and rocuronium.

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1. Introduction

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction in which mast cells and basophils play a major role through the release of mediators. Although anaphylaxis during anesthesia is rare, it cannot be avoided. The literature reports a frequency of 1 in 3500 to

[☆] Disclosures: The authors have no funding sources or competing interests to disclose.

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20 000 [1] with a mortality rate of 3% to 9% [2], and an additional 2% surviving with severe brain damage [3]. The most common cause of anaphylaxis during general anesthesia is the use of neuromuscular blocking agents (NMBAs). Among the NMBAs, rocuronium has been identified in a number of studies as the agent most commonly associated with anaphylaxis [1,4]. Sugammadex, which was specifically designed for the reversal of rocuronium-induced neuromuscular block, has also been known to result in hypersensitivity reactions and anaphylaxis [5]. We report herein a rare case of successive anaphylactic reactions to sugammadex and rocuronium during anesthesia in different surgeries. Consent for publication of this letter was obtained from the patient.

2. Case report

A 19-year-old woman (50 kg, 160 cm) was injured in a fall in a suicide attempt. She was scheduled for urgent posterior spinal fusion of the lumbar vertebra fracture. The patient had no history of surgery. She was on medications for depression and asthma, and had also been diagnosed with allergy to house dust mites. General anesthesia was induced by intravenous administration of fentanyl, remifentanyl, and propofol, with rocuronium administered for neuromuscular blockade. Anesthesia was maintained with propofol, remifentanyl, and rocuronium. Cefazoline and flurbiprofen were also administered. The surgery was completed uneventfully. At the end of surgery, sugammadex was administered slowly to antagonize residual neuromuscular blockade. Five minutes after administration of sugammadex, airway pressure showed a rapid elevation, and values of end-tidal CO₂ and peripheral oxygen saturation (SpO₂) decreased. Bronchospasm was diagnosed by revealing wheezing. The patient developed intense erythema over the anterior chest and face. Systolic blood pressure decreased from 100 to 50 mmHg, and heart rate increased to 140 beats/min. Since anaphylaxis caused by sugammadex was suspected, she was treated with intramuscular epinephrine and rapid infusion of crystalloid. These treatments improved systolic blood pressure to approximately 90 mmHg. Hydrocortisone was also administered and the patient was transferred to the intensive care unit. Mechanical ventilation was performed under propofol and fentanyl for sedation. The trachea was extubated uneventfully 3 hours later, when no further wheezing or erythema was apparent. Ten days later, a second general anesthesia was carried out for calcaneal fracture without NMBAs, and proceeded uneventfully.

Twelve days after the trauma, a third general anesthesia was scheduled for anterior spinal fusion to reinforce the spinal column. General anesthesia was induced with propofol, remifentanyl, and rocuronium. Following tracheal intubation (8 minutes after administration of rocuronium),

sinus tachycardia developed to 120-130 beats/min and blood pressure decreased to 70/30 mmHg. Airway pressure elevated to 40 cmH₂O with lung wheezing and erythema. SpO₂ decreased to 80% under 100% oxygen inhalation. Anaphylaxis was suspected and intramuscular epinephrine was thus administered. Hydrocortisone and crystalloid were also administered. The surgery was cancelled and she was transferred to the intensive care unit under propofol sedation. About 30 min after this anaphylactic reaction, blood examination was performed (Table 1). Plasma histamine levels were elevated, but serum tryptase levels remained normal. She was extubated uneventfully 3 h later.

Nineteen days after trauma, the fourth general anesthesia for anterior spinal fusion was performed. Because rocuronium was considered as the most likely causative agent for the anaphylactic reaction, we planned to use no NMBAs. General anesthesia was induced and maintained with propofol, sevoflurane, and remifentanyl. The operation was completed uneventfully.

Fourteen weeks after the last anaphylaxis event, we consulted a dermatologist. Skin prick tests were performed using 1:1000, 1:100, 1:10 and 1:1 dilutions of both rocuronium (10 mg/ml) and sugammadex (100 mg/ml). Skin prick tests for rocuronium and sugammadex both yielded negative results. However, on intradermal testing (IDT), 1:1000 dilutions of rocuronium and undiluted sugammadex yielded positive reactions. She also underwent drug-induced lymphocyte stimulation testing, but all results were negative. Positive reactions to IDT suggested sugammadex and rocuronium as the causative agents of anaphylaxis. She was diagnosed with anaphylactic reactions to both sugammadex and rocuronium. Immunochemical evidence of IgE-mediated reaction was confirmed with IDT. She refused further investigation to identify agents that are less likely to cause anaphylaxis on subsequent exposure and discharged.

3. Discussion

In cases of anesthesia-related anaphylaxis, NMBAs appear responsible for 50% to 70% of cases, followed by reactions to latex and antibiotics [2]. To the best of our knowledge, this is the first report in a patient with successive anaphylactic reactions to both sugammadex and rocuronium during anesthesia.

Table 1 Results of blood sample investigations carried out 30 min after an anaphylactic event

Test carried out	Value	Normal range
Histamine (μg/L)	3.94	0.125-1.23
Tryptase (μg/L)	4.4	0-11.4
Complement C3 (g/L)	1.49	0.8-1.65
Complement C4 (g/L)	0.3	0.12-0.3
Total IgE (U/L)	0.299	0-0.173

Rocuronium seems to be the agent most frequently involved in perioperative anaphylaxis [1,4]. Substituted ammonium ions have been proposed as the common allergenic epitope, and are responsible for the neuromuscular blocking effects of NMBAs, including rocuronium. Common environmental chemicals share these allergenic epitopes with NMBAs [5]. In our case, sensitization to rocuronium was likely to have been triggered by the first surgery. As a result of the presence of substituted ammonium ions, significant cross-reactivity exists between NMBAs [2]. The highest rate of cross-reactivity was shown with rocuronium and other NMBAs (80%) [1].

Sugammadex is a modified γ -cyclodextrin and a selective binding agent that is used to reverse neuromuscular blockade by encapsulating rocuronium as an included complex, thus moving it from the neuromuscular junction to the plasma. Sugammadex has been available in Japan since 2010 and in the European Union since 2009. However, in the United States, the Food and Drug Administration has expressed concerns regarding the potential for hypersensitivity and allergic reactions; therefore, clinical use of sugammadex has not yet been approved in the United States [6]. Several cases of anaphylaxis in response to sugammadex have been reported [7,8]. Because some drugs, foods, and common environmental chemicals containing cyclodextrins in the product formulations show cross-sensitivity [9], previous sensitization could lead to anaphylaxis on first exposure to sugammadex [4].

Skin tests represent the gold standard for the detection of suspected causative agents for anaphylaxis [2]. Most experts advise postponing skin tests by 6 weeks or more after the last episode of anaphylaxis to avoid false-negative results [10]. When skin tests show positive results for rocuronium, avoiding other NMBAs is advised due to the high risk of cross-reactivity (approximates 60-70%) among NMBAs [2]. Some authors have considered that the inappropriately high concentrations of suspected drugs used in IDT may induce false-positive results [11]. In our case, only the 1:1000 dilution of rocuronium showed positive results in IDT. Positive IDT with a 1:1000 dilution of rocuronium in anaphylactic patients appears highly reliable [11]. In the present study, the recommended concentration of IDT with sugammadex remains unclear.

In acute systemic allergic reactions, mast cells and basophils play important roles. Mediators such as histamine and tryptase released from these cells may offer very useful indicators [1]. The magnitude of elevation of these mediators is linked to the severity of anaphylaxis; however, normal levels of these mediators do not absolutely exclude the diagnosis [12]. Blood samples should be drawn between 15 and 60 min for grade 1 or 2, and 30 and 120 min for grade 3 or 4 hypersensitivity reaction after the anaphylactic event [11].

When rocuronium-induced anaphylaxis that is unresponsive to traditional treatments is greatly suspected, some case reports have demonstrated that sugammadex may be chosen as another therapeutic option [13]. Although one plausible

mechanism is the encapsulation of the antigenic rocuronium epitope by sugammadex, whether sugammadex would be of benefit for rocuronium-induced anaphylaxis remains unclear [14]. According to the present case, clinicians should be reminded that use of sugammadex in these situations is an unlicensed indication and may result in another episode of anaphylaxis.

In conclusion, we have provided the first report of successive episodes of anaphylaxis in response to sugammadex and rocuronium during anesthesia. We suspected anaphylaxis based on not only clinical manifestations and biochemical test results, but also positive results of IDT for both drugs. Anesthetic management was successful without NMBAs in the ensuing surgery. We must be aware that anaphylaxis can be induced by both sugammadex and rocuronium.

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