Two Cases of Rocuronium-Induced Anaphylaxis/Anaphylactic Shock Successfully Treated With Sugammadex

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While anaphylaxis can occur at any time during general anesthesia, 90% of cases occur at induction of anesthesia. As several drugs are administered simultaneously at this time, it is difficult to identify the causative agent. However, it has been found that rocuronium is the most common drug associated with perioperative anaphylaxis. We treated 2 cases of patients who were administered sugammadex for anaphylactic symptoms thought to be caused by rocuronium, after which the anaphylactic symptoms disappeared. One of the most important aspects of treating anaphylactic shock is improving hemodynamics. If signs indicating circulatory collapse are observed, epinephrine should be administered immediately. However, because rocuronium was suspected of being the causative agent, and taking the patients' clinical course over time into consideration, sugammadex was initially administered. As a result, symptoms improved. Therefore, we believe that the administration of sugammadex may be effective for treating anaphylaxis caused by rocuronium and also help in identifying the causative agent.

Key Words: Sugammadex; Anaphylactic shock; Rocuronium; Epinephrine.

Anaphylactic shock, a severe complication during general anesthesia, is a rapidly occurring severe allergic reaction that may be fatal. Causative agents include drugs, foods, insects, latex, and even exercise. The incidence of allergic reactions due to drugs is 1% to 3% of exposures, but the frequency of anaphylaxis is much lower.¹ The frequency of anaphylaxis during general anesthesia has been reported to be between 1:5,000 and 20,000 cases. Muscle relaxants are the most common causative drugs during general anesthesia, and it is estimated that there is 1 case for every 6,500 administrations.² Rocuronium is thought to have the highest frequency of allergic reactions.³

We report 2 cases of anaphylaxis/anaphylactic shock believed to be induced by rocuronium, in which

anaphylactic symptoms disappeared following administration of sugammadex and for which remission was achieved without further complications.

In preparing this report, written consent for this publication was obtained from the patient herself (case 1) and from the patient and her parents (case 2).

CASE PRESENTATION

Case 1

The patient was a 38-year-old woman (height: 156 cm, weight: 48 kg) with a diagnosis of synovial osteochondromatosis of the left temporomandibular joint. She was scheduled for left temporomandibular joint contrast radiography and tumorectomy.

Her medical history was unremarkable. Preoperative evaluation was normal except for decreased mouth opening, with the remainder of the airway examination otherwise unremarkable. No difficulty was expected with mask ventilation.

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Table 1. Clinical Criteria for Diagnosing Anaphylaxis*

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minute to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) AND at least 1 of the following:
 - A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - B. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - A. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - C. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
 - A. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - B. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

* BP indicates blood pressure; PEF, peak expiratory flow.

Prior to anesthesia, Urografin Inj 60% (a hyperosmolar ionic contrast agent, amidotrizoic acid) was injected into the temporomandibular joint to perform contrast radiography. Anesthesia was then rapidly induced with 100% oxygen, 100 µg of fentanyl, and propofol at a target blood concentration 6 µg/mL followed by 30 mg (0.625 mg/kg) of rocuronium. Propofol target concentration was decreased to 4 µg/mL (~140 µg/kg/min) and maintained after the induction of general anesthesia. Since trismus was observed preoperatively, nasal intubation with a fiberoptic was performed. However, the endotracheal tube was removed because of esophageal intubation, and manual mask ventilation was performed. At that time, redness appeared on the anterior thorax, spreading from the abdomen to the thighs and the face. A bulging rash also appeared on the thighs. Although blood pressure had not decreased (95/65 mm Hg), the patient's heart rate was elevated at 150 beats/min. Therefore, according to the clinical diagnostic criteria of anaphylaxis⁴ (Table 1), anesthesia induction agent-induced anaphylaxis was suspected, so the continuous administration of propofol was discontinued, and 375 mg of methylprednisolone was administered by rapid infusion. We simultaneously obtained a blood sample. Manual mask ventilation was smooth, and there were no abnormal respiratory

sounds. Sugammadex 200 mg (~4 mg/kg) was administered as an antagonist of rocuronium, upon which cutaneous symptoms were alleviated and heart rate decreased to 90 beats/min. Blood pressure was 110/50 mm Hg, and it did not decrease thereafter. After restarting spontaneous respiration, the surgery was suspended, and the patient awakened rapidly without hemodynamic instability. Because of concerns of possible biphasic anaphylaxis, the patient was transferred to a third-party medical institution. However, no abnormalities were observed, and the patient was discharged the following day. Two months later, a drug-induced lymphocyte stimulation test was performed. Propofol and rocuronium tested negative, but Urografin Inj 60% and fentanyl were positive.

Case 2

The patient was an 18-year-old woman (height: 158 cm, weight: 52 kg) with a diagnosis of bilateral hypertrophy of the masseter muscles with bilateral mandibular angle hypertrophy. She was scheduled for bilateral reduction of the masseter muscles and bilateral plastic operation of the mandibular angle. Her medical history and preoperative evaluation were unremarkable. Rapid anesthetic induction was with 100% oxygen, 100 µg of fentanyl, remifentanyl at 0.3 µg/kg/min, 110 mg propofol, and 40 mg (0.77 mg/kg) rocuronium. Nasal intubation was performed and mechanical ventilation started. Redness appeared on the anterior thorax after intubation, blood pressure decreased to 65/30 mm Hg, and heart rate increased to 100 beats/min. Continuous administration of remifentanyl was discontinued, and an attempt was made to raise blood pressure with 4 mg of ephedrine. However, as hemodynamics did not improve, and redness spread from the abdomen to the thighs and then the whole body, the patient was diagnosed with anaphylactic shock induced by induction drugs according to the clinical diagnostic criteria of anaphylaxis.² Skin symptoms were redness only, and no urticaria was observed. To raise blood pressure, another peripheral vein route was secured. Rapid crystalloid infusion was started, and 125 mg of methylprednisolone was administered. SpO₂ decreased to 96% at one point, so respiration was converted to manual ventilation, with SpO₂ rapidly recovering to 99%. There were no abnormal respiratory sounds. The surgery was suspended and, based on the assumption that rocuronium was the most likely causative agent,¹ as well as our experience with case 1, 200 mg (~4 mg/kg) of sugammadex was administered. This resulted in a reduction of cutaneous symptoms and improvement in

Table 2. Substances Responsible for IgE-Mediated Perioperative Hypersensitivity Reactions in France (Results in Percentages From 7 Consecutive Surveys)*

	1984–1989 <i>n</i> = 821	1990–1991 <i>n</i> = 813	1992–1994 <i>n</i> = 1030	1994–1996 <i>n</i> = 734	1997–1998 <i>n</i> = 486	1999–2000 <i>n</i> = 518	2001–2002 <i>n</i> = 502
NMBAs	81	70.2	59.2	61.6	69.2	58.2	54
Latex	0.5	12.5	19	16.6	12.1	16.7	22.3
Hypnotics	11	5.6	8	5.1	3.7	3.4	0.8
Opioids	3	1.7	3.5	2.7	1.4	1.3	2.4
Colloids	0.5	4.6	5	3.1	2.7	4	2.8
Antibiotics	2	2.6	3.1	8.3	8	15.1	14.7
Other	2	2.8	2.2	2.6	2.9	1.3	3
Total	100%	100%	100%	100%	100%	100%	100%

* *n* indicates the number of cases. Modified and quoted from Mertes PM, Laxenaire MC. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France. *Annfr Anesth Reanim.* 2004;23(12):1133–1143.

hemodynamics. After waking, we confirmed sufficient spontaneous respiration and stable hemodynamics, inserted a tube exchanger, and extubated the patient. She was observed for a period in the operating room and, as there were no respiratory or hemodynamic abnormalities, the tube exchanger was removed, and the patient was returned to the hospital ward. After leaving the operating room, blood pressure, electrocardiogram, SpO₂, and body temperature were monitored for 24 hours. No biphasic anaphylactic response occurred, and the patient was discharged 2 days later. The patient later refused allergist evaluation to determine the causative agent.

DISCUSSION

Anaphylaxis is roughly divided into immunologic (IgE-mediated) and nonimmunologic (non-IgE-mediated) types. The nonimmunologic type has been referred to in the past as “anaphylactoid” reaction, but in recent years, this name is less used and tends to be bundled with anaphylaxis. In case 1, the contrast injection was the first exposure for the patient, and in both cases 1 and 2, general anesthesia agents were first-time administrations for these patients. It is thought that the cause of allergies to muscle relaxants is due to their quaternary ammonium structure. This structure is also included in some cosmetics, toothpastes, shampoos, and other common products. It is possible that one might first be sensitized by being exposed to them in our daily lives. Thus, initial use of rocuronium could trigger anaphylaxis.⁵

During general anesthesia, there are numerous opportunities for patients to come into contact with potential allergens such as drugs, blood components contained in transfusions, and latex. Although anaphylactic shock can occur at any stage of general anesthesia, 90% of cases occur during induction of anesthesia.⁶ As

multiple drugs are administered almost simultaneously during the induction of anesthesia, it is difficult to identify the causative drug. However, muscle relaxants are the most common causative drugs, followed by latex and antibacterial drugs (Table 2). Rocuronium has been shown to have the highest frequency of allergy among the muscle relaxants.³ Rocuronium was suspected to be the cause of anaphylaxis in both cases 1 and 2, considering the time course.

In case 1, intra-articular contrast agent was used before induction of anesthesia. In Japan, cancer chemotherapy drugs are the most common cause of drug-induced anaphylaxis, followed by radiologic contrast agent.⁷ Therefore, the contrast agent should also be considered as the cause of anaphylaxis in case 1. The frequency of allergic reaction by intravenous ionic contrast agent and hyperosmolarity is high. However, the rate of anaphylactic shock from intra-articular contrast administration is only 0.003%,⁸ and allergic reaction by administering Urografin Inj 60% to a joint has not been reported so far. Also, in drug-induced anaphylaxis, the median time from antigen exposure to circulatory collapse is 5 minutes.⁹ In case 1, about 10 minutes elapsed from completion of the contrast examination until induction of anesthesia, and anaphylaxis occurred 2 minutes after administration of rocuronium. Because of the time course, we felt that the contrast agent was an unlikely cause of the anaphylactic shock.

As a result of blood collection very shortly after onset of symptoms, an increase in plasma tryptase (22.9 µg/L) and hematocrit (40.3%) and a disappearance of basophils were observed. Furthermore, the regression of the symptoms was confirmed 1 minute after sugammadex administration. Therefore, we presumed that rocuronium was the causative drug. However, from the results of a drug-induced lymphocyte stimulation test at a later date, the possibility of involvement of delayed type hypersensitivity reaction by fentanyl and/

or Urografin Inj 60% was also considered. It should be noted that not all cases of rocuronium sensitivity are diagnosed with the drug-induced lymphocyte stimulation test, and a drug provocation test would be required to rule out rocuronium allergy.¹⁰

Improving hemodynamics is one of the most important treatments in anaphylactic shock, and any signs of imminent circulatory collapse should be treated immediately by administering epinephrine.³ Park et al¹¹ also recommended epinephrine as the first-choice drug. Indications for epinephrine administration are based on the severity of anaphylaxis symptoms (eg, hypotension, unconsciousness, respiratory symptoms or compromise, cyanosis, arrhythmia, cardiac arrest, dysphagia, intolerable persistent abdominal pain, and repeated vomiting).

The symptoms of case 1 were cutaneous symptoms and sustained tachycardia, whereas respiratory symptoms and hypotension were not observed. Therefore, epinephrine was not administered, and the second-line agent, methylprednisolone, was administered instead. When the rocuronium antagonist sugammadex was then administered, the cutaneous symptoms were alleviated, and the patient's heart rate decreased immediately following administration. Therefore, we presumed that rocuronium-induced anaphylaxis had occurred. Respiratory symptoms are observed in 70% of anaphylactic shock cases.¹² Fortunately, respiratory symptoms did not appear at the onset of anaphylaxis in this case, and manual ventilation with a mask was unremarkable. However, if respiratory symptoms had appeared, manual ventilation by a mask was difficult, or hypotension developed, simultaneous administration of sugammadex and epinephrine would have been chosen.

The reddening in case 2 appeared on the anterior thorax immediately after intubation. We assumed that the high dose of opioids in combination with propofol at the induction of anesthesia caused hypotension, with tachycardia probably occurring as compensation. The continuous administration of remifentanyl was interrupted, and an attempt was made to increase blood pressure with ephedrine. However, as the low blood pressure was not alleviated and the redness spread to the whole body, the patient was diagnosed with anaphylactic shock induced by anesthesia induction agents. Cutaneous symptoms, sustained tachycardia, sustained hypotension, and decreased SpO₂ were also observed. It is possible that in this case, epinephrine should have been administered as the first-choice drug. However, we were concerned that it could cause excessive cardiovascular stimulation, and manual ventilation was not difficult with rapid return of normal oxygenation. Furthermore, as rocuronium is the causative drug associated with the highest rates of perioperative

anaphylactic shock,³ and based on our experiences with case 1, we thought that symptoms might improve with administration of sugammadex. Therefore, we administered sugammadex rather than epinephrine. After administering sugammadex, the cutaneous symptoms were alleviated immediately, and the patient's hemodynamics also stabilized. Therefore, we presumed that this was a case of rocuronium-induced anaphylactic shock. If respiratory symptoms were more severe and manual ventilation were difficult, epinephrine would have been administered first.

Rapid volume expansion is also one of the initial treatments for anaphylaxis, as vasodilatation and hyperpermeability of capillary vessels occur simultaneously in anaphylaxis. This can rapidly decrease circulating blood volume. For this reason, rapid volume infusion according to circulatory dynamics is important.¹³ In case 2, we secured another peripheral vein route for more rapid volume infusion.

In both cases, we were also concerned with biphasic anaphylaxis, so the patients were hospitalized after anesthesia. Biphasic anaphylaxis occurs in about 23% of adult cases. It is reported to occur up to 72 hours after the first reaction.¹³ There is no clear standard, however, for the postevent monitoring period at present.

Some previous reports have described the effective use of sugammadex for rocuronium-induced anaphylactic shock.^{14–17} One of these reported that circulatory symptoms did not improve despite multiple administrations of epinephrine but improved by administration of sugammadex.¹⁴ Kawano and Yokoyama¹⁸ theorized that the mechanism of sugammadex in reversing presumed anaphylaxis to rocuronium is the rocuronium molecule's quaternary ammonium group being enclosed by sugammadex, thereby eliminating the antigenicity of rocuronium. However, even if this antigenicity could be completely antagonized, it may not inhibit the anaphylactic reaction that is already in course.¹⁷ As such, it is important not to neglect the necessity of steroid administration or the use of epinephrine, which are standard treatments for anaphylactic shock, based on clinical presentation.

Interestingly, sugammadex itself can also cause anaphylaxis. Therefore, it is not yet standard practice that sugammadex should be selected for initial therapeutic use for perioperative anaphylaxis at anesthetic induction when rocuronium has been administered. The first-line drug would still be considered to be epinephrine, with supporting therapies such as intravascular fluids, corticosteroids, and antihistamines. However, if rocuronium is thought to be the likely agent of impending allergic response in a relatively stable patient, sugammadex can be considered. If symptoms do not resolve, standard therapy should not be deferred. For

serious signs of anaphylaxis, when response to epinephrine treatment according to guidelines is not satisfactory, sugammadex should be considered an option.

In conclusion, we treated 2 cases in which anaphylaxis/anaphylactic shock occurred upon induction of anesthesia. Considering the possibility that rocuronium was the causative drug, we administered sugammadex, which improved symptoms in both cases. These results suggest that the administration of sugammadex may be effective for rocuronium-induced anaphylaxis and that it may also be effective for identifying the cause of such cases.

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