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Suspected anaphylactic reaction associated with sugammadex
-a case report-

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We describe a case of a 35-year-old male patient who was scheduled for laparoscopic cholecystectomy and developed a life-threatening anaphylactic reaction 2 min after the administration of sugammadex. He manifested erythematous wheals on the entire body, dyspnea, hypotension, and tachycardia. These symptoms disappeared after the administration of epinephrine. The patient recovered and was discharged at postoperative day 5 without any complications. After 7 weeks, we performed a skin prick test, and there was a weakly positive reaction for sugammadex. This case is suspected anaphylaxis associated with sugammadex, and we need to be aware that the use of sugammadex is associated with a serious risk of anaphylaxis.

Key Words: Anaphylaxis, Sugammadex.

Anaphylaxis in the perioperative period is a life-threatening adverse event. Although it is a rare event during anesthesia (1 in 3500–13000), it can significantly increase mortality and morbidity. It is difficult to diagnose early because the symptoms of anaphylaxis can be attributed to other causes during anesthesia. Therefore, the number of cases of perioperative anaphylaxis is significantly underestimated [1].

Sugammadex is a gamma-cyclodextrin that is widely used as an antagonist to aminosteroid neuromuscular blockade. In Korea, it has been used since February 2013, and its safety has been well tolerated [2]. However, in the United States, the Food and Drug Administration has not yet approved its use due to the possibility of anaphylactic reactions. Several cases of anaphylaxis associated with sugammadex were reported in nations where sugammadex is widely used [3]. However, to our knowledge, sugammadex has not yet been reported to be associated with anaphylaxis in Korea.

Therefore, we present a case of a patient who presented with generalized erythema, dyspnea, and cardiovascular shock associated with sugammadex administration during reversal of neuromuscular blockade.

Case Report

A healthy 35-year-old man was scheduled for laparoscopic cholecystectomy under general anesthesia for acute cholecystitis. His weight was 109 kg, and his height was 182 cm. He had a history of asthma and allergy to animal hair and was treated with a salbutamol inhaler 3 years prior, but showed no symptoms recently. Additionally, he had no surgical or anesthetic history. Physical and pre-anesthetic examinations, including a chest X-ray, electrocardiography (ECG), laboratory results, and a pulmonary function test were unremarkable.

The patient received tazobactam intravenously for preven-

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tive antibiotics and glycopyrrolate (0.2 mg) intramuscularly for premedication 30 min before the operation. At arrival to the operating room, standard monitoring included non-invasive blood pressure, ECG, and peripheral oxygen saturation (SpO_2). The patient's initial blood pressure was 155/85 mmHg, heart rate was 70 beats/min, and SpO_2 level was 99%.

General anesthesia was induced with 1% propofol (150 mg) with lidocaine (40 mg) pretreatment and continuous infusion of remifentanil (0.1–0.5 μg/kg/min). After the patient was asleep, rocuronium (80 mg) was administered intravenously and, after 1 min, his trachea was intubated successively. Next, anesthesia was maintained with sevoflurane, and his vital signs, including blood pressure, heart rate, and SpO_2, were maintained stably during the operation. Fifty minutes after starting anesthesia, efforts of self-ventilation were shown, and we administered additive rocuronium (10 mg). Ten minutes before the end of the surgery, we administered fentanyl (100 μg) and discontinued remifentanil. The operation was finished within 90 min without complication. At the end of surgery, at a train of four (TOF) count of 3, we administered sugammadex (200 mg; about 1.8 mg/kg) to antagonize neuromuscular blockade intravenously. Two minutes after sugammadex administration, his TOF ratio was recovered to 0.9, and he could breathe spontaneously. At that time, we discovered an erythematous wheal in his anterior thorax that was considered strange but not serious, and decided to extubate. After extubation, the erythematous wheal gradually spread to the entire body. Soon after, he complained of dyspnea, his blood pressure decreased to 85/40 mmHg, his heart rate was 130 beats/min, SpO_2 level was 83%, and bilateral wheezing was demonstrated on chest auscultation. We administered dexamethasone (15 mg) and dexchlor-pheniramin (4 mg) intravenously, and a salbutamol nebulizer (5 mg) with 6 L/min of 100% oxygen via face mask was inhaled. Despite these interventions, his symptoms did not improve, his blood pressure decreased further to 65/38 mmHg, his heart rate was 135 beats/min, and SpO_2 level was 83%. Our suspicion of an anaphylactic reaction increased; thus, epinephrine infusion (0.06 μg/kg/min) was started after an intravenous epinephrine bolus (20 μg), and 100 ml of fluids was administered over 10 min. At that time, arterial blood gas analysis (pH 7.277; pCO_2, 28.7; pO_2, 63.3; HCO_3, 13.1; BE, −12.1) and chest radiography, which showed no active lesion on the chest radiographic image, were performed. Within 10 min, his vital signs gradually increased to 105/55 mmHg, his heart rate was 105 beats/min, SpO_2 level was 95%, and his generalized erythema and tachypnea disappeared. After an additional 10 min, his blood pressure increased to 138/59, his heart rate was 90 beats/min, and SpO_2 level was 98%. The patient's vital signs continued to remain stable, and we discontinued the epinephrine infusion and transferred the patient to the intensive care unit. After half of the day, he was transferred to the general ward without any complication, and was discharged satisfactorily 5 days after surgery. We recommended laboratory testing for anaphylaxis and the skin prick test. Total IgE and specific IgE for antibiotics were examined. The patient's total IgE was 194 kU/L (reference, < 100 kU/L) and specific IgE for antibiotics were all negative, but he refused the serum tryptase test. After 7 weeks, skin prick tests for sugammadex, rocuronium, and fentanyl were performed, and the result was weakly positive for only 1 : 1 sugammadex (3 × 2 mm) compared with the positive (histamine; 5 × 5 mm) and negative (normal saline; negative) controls, but negative in 1 : 10, 1 : 100, 1 : 1000 sugammadex and all concentrations of fentanyl and rocuronium. Based on the time course of the event, anaphylactic reaction associated with sugammadex was strongly suspected.

Discussion

Anaphylaxis is defined as "a serious, life-threatening, generalized or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death" [4]. The diagnosis of anaphylaxis is mainly based on the clinical course because the course rapidly deteriorates, as mentioned in the definition [4]. The most common clinical manifestations are cardiovascular symptoms such as hypotension, tachycardia or bradycardia, cardiovascular collapse, bronchospasm, and mucocutaneous symptoms such as erythema, edema, urticaria, and angioedema. Cardiovascular shock in anaphylaxis was reported as 41% [5]. In our case, after 2 min of sugammadex administration, the patient had generalized erythematous wheals, dyspnea, and progressive cardiovascular shock. The clinical features in our case were similar to those in previous cases. This case met World Anaphylaxis Organization criteria for anaphylaxis, and the severity grade using the severity scale was grade III [4].

It is difficult to identify the cause of anaphylaxis during anesthesia because various drugs are used. The most common cause of perioperative anaphylaxis is neuromuscular blocking agents (69.2%), latex (12.1%) and antibiotics (8%). Sedatives, analgesics, local anesthetics, and other drugs are less frequent causes [1]. In our patient, antibiotics were administered without complication 30 min before surgery, and other drugs such as neuromuscular drugs and opioids were administered 20 min before the anaphylactic reaction. Only sugammadex was administered 2 min before the anaphylactic reaction.

Elevation of serum tryptase and histamine levels is useful to confirm the diagnosis of anaphylaxis [1,4]. However, serum and urine histamine tests are not available in Korea. The serum tryptase test has a positive predictive value of 93% and a negative predictive value of 54%, and should be performed within 6 h because of its short half-life [1]. However, in our case, the serum tryptase test was not performed because of the patient's

refusal.

The detection of specific IgE antibodies using the *in vivo* IgE test (skin prick test or intradermal test) and *in vitro* IgE test is useful to identify the cause of the allergic reaction [1,4]. The skin prick test is more sensitive than *in vitro* tests and is generally used but remains unvalidated [4]. There is no absolute agreement on the concentration of sugammadex to be used. In British Society or Allergy and Clinical Immunology, the use of 1 : 10 diluted or undiluted agent is recommended for anaphylaxis associated with perioperative agents. A positive decision is made when the wheal diameter with a 1 : 10 dilution is at least 2 mm greater than the negative control. However, a positive wheal to only undiluted agent may be considered a positive decision when the clinical course is fitted to the agent and other causes are ruled out [6]. Fourteen cases of anaphylaxis associated with sugammadex reported a positive result of the skin prick test or intradermal test [3,7-10]. Soria et al. [9] reported a positive intradermal test with 1 : 1000 sugammadex, although the patient showed a positive skin prick test only with undiluted sugammadex at 30 min. In our case, we had a weakly positive skin prick test to undiluted sugammadex, but an intradermal test was not recommended because of concern regarding the potential risk of anaphylaxis. *In vitro*-specific IgE for antibiotics were also examined, and the result was negative.

When anaphylaxis is suspected, turning off the responsible agent and administering appropriate treatment promptly are important. Epinephrine is the drug of choice for anaphylaxis because it maintains blood pressure with an α1 adrenergic effect and relaxes the bronchial smooth muscle with a β_2 adrenergic effect [1,4]. In our case, the use of intravenous epinephrine rapidly improved the patient's symptoms.

Sugammadex is a modified gamma-cyclodextrin that is used as an antagonist to aminosteroid neuromuscular blockade, and has been used since February 2013 in Korea. Sugammadex is an innovative agent that has a rapid recovery time and rapid renal clearance. It provides several advantages, including avoidance of cardiovascular side effects associated with neostigmine, avoidance of postoperative residual curarization, and reversal of deep neuromuscular blockade [11]. It has reported good tolerance in Korea [2].

However, in the United States, the Food and Drug Administration has not yet approved sugammadex due to the possibility of anaphylactic reactions. Several cases of hypersensitivity reactions associated with sugammadex have been reported in countries that frequently use the drug. These reactions appear to be more frequent at higher clinical doses [12]. However, Godai et al. [7] reported three cases, although they used 1.9–2.2 mg/kg low-dose sugammadex.

Cases of sugammadex-induced anaphylaxis have been reported more frequently in Japan because sugammadex is widely used. To our knowledge, thirteen cases of anaphylaxis associated with sugammadex have been reported until now in Japan [3,7,8,13,14]. However, to our knowledge, there is no reported case of anaphylaxis to date in our country.

Two issues need to be addressed regarding this case. First, our patient had an allergic asthmatic history. Amao et al. [15] reported that two patients with an asthma history showed bronchospasm associated with sugammadex. Five cases of anaphylactic reaction associated with sugammadex had reported an asthma or allergic history [3]. Allergic patients may have been predisposed to anaphylaxis to sugammadex. However, most patients with anaphylaxis associated with sugammadex have no history of sugammadex exposure. It has been suggested that the use of cyclodextrins in food may result in sensitization to sugammadex [3]. We suggest that strict caution should be applied when considering sugammadex administration in asthmatic and allergic patients.

Second, the use of sugammadex is likely dangerous because it's associated anaphylactic reaction appears at the time of extubation and movement to the postanesthetic care unit or intensive care unit when the patients are less monitored. Therefore, we suggest that vigilance after sugammadex administration is necessary.

In summary, we present a case of a patient who presented with generalized erythema, dyspnea, and cardiovascular shock 2 min after sugammadex administration; the case was confirmed to be anaphylaxis associated with sugammadex by a positive skin test. We ruled out other causes using specific IgE for antibiotics and a negative skin prick test for rocuronium and fentanyl, as well as the clinical course of the event (they were administered 20 min before the event).

This is a suspected case of hypersensitivity reaction associated with sugammadex reported for the first time in Korea. We need to be aware that the use of sugammadex is associated with a serious risk of anaphylaxis.

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