A suspected case of sugammadex-induced anaphylactic shock
-A case report-

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We describe a case involving a 69-year-old woman who developed anaphylatic shock caused by a clinical dose of sugammadex (2 mg/kg, 100 mg intravenously) 5 minutes after its administration. She developed redness and welts all over her body, and complained of an oropharyngeal itching sensation with dyspnea and dizziness. Her vital signs were closely monitored. She also experienced a sudden onset of hypotension (from 110/70 to 49/40 mmHg) and tachycardia (from 75 to 120 bpm). We diagnosed anaphylactic shock on the basis of these clinical manifestations. After 20 min of traditional treatment (hydration, ephedrine, cortisol, and phenylephrine), her vital signs returned to normal. No postoperative complications were evident, and the patient was discharged from the hospital. Although the prevalence of anaphylactic reactions to sugammadex is rare, physicians using sugammadex should be aware of the possibility of sugammadex-induced anaphylaxis. (Anesth Pain Med 2015; 10: 288-290)

Key Words: Anaphylactic shock, Hypersensitivity, Sugammadex.

Sugammadex, discovered at the Newhouse research site [1], is increasingly being used for reversal of steroidal neuromuscular blocking agents in general anesthesia. As a modified \( \gamma \)-cyclodextrin, sugammadex exerts its effect by forming tight water-soluble complexes at a 1:1 ratio with steroidal neuromuscular blocking drugs, especially rocuronium and vecuronium [2,3]. During rocuronium-induced neuromuscular blockade, intravenous administration of sugammadex creates a concentration gradient that favors the movement of rocuronium molecules from the neuromuscular junction back into the plasma, resulting in rapid recovery of neuromuscular blockades. Sugammadex exerts its effects about 10 times faster than neostigmine, without the need for concomitantly administered atropine, and is generally thought to be relatively safe, partly due to its lack of adverse effects [4,5]. However, there have been recent case reports of allergic reactions to the clinical doses of sugammadex.

We report a case of suspected sugammadex-induced anaphylactic shock, the first in Korea.

**CASE REPORT**

The patient was a 69-year-old woman (weight: 50 kg; height: 158 cm) who underwent extensive resection of varicose veins. She had no major medical co-morbidities and neither smoked nor drank alcohol. She had received general anesthesia 6 years earlier for treatment of a right foot fracture, without complications. She had never experienced allergic reactions related to medication, food, or other environmental factors. Upon arrival in the operating room, her baseline vital signs were as follows: blood pressure (BP): 111/70 mmHg; heart rate (HR): 65 bpm; and oxygen saturation: 100%. One gram of cefazedone was administered preoperatively after either an intradermal test or as part of the induction sequence. Anesthesia was induced with 200 mg of pentothal sodium. Once loss of consciousness was achieved, 40 mg (0.80 mg/kg) of rocuronium was administered. Two minutes later, her trachea was intubated.

Anesthesia was maintained with 2% sevoflurane and a 50% oxygen-nitrous oxide mixture. During the surgery, the bispectral index, oxygen saturation, and end-tidal CO\(_2\) were maintained within normal ranges. The BP was maintained between 170/100 and 90/40 mmHg, and HR between 65 and 90 bpm. The total operation time was 60 min. After checking that the
train-of-four count was reached at 2, 2 mg/kg of sugammadex was injected to antagonize the neuromuscular blockade. No other drug was given at this time. Three minutes after the injection of sugammadex, the patient was extubated when she was able to breathe spontaneously. Five minutes after extubation (2 min after transfer to the recovery room), the patient demonstrated redness and indicated symptoms of oropharyngeal itching, and palpitations, but she did not complain about dyspnea. At this point, her BP fell to 49/30 mmHg, and she developed tachycardia of between 110 and 120 bpm; however, 100% oxygen saturation was maintained using a 5 L/min oxygen mask in the recovery unit. Suspecting a possible anaphylactic reaction to sugammadex, she was treated with hydration (2 L crystalloid), 100 mg of hydrocortisone, 10 mg of ephedrine, and a cumulative dose of 1,450 μg of phenylephrine (bolus 200 μg and intravenous infusion of 0.5 μg/kg/min for 50 min). The intravenous infusion was tapered gradually, by 0.2 μg/kg/min, for 20 min.

After 70 min of this treatment, her BP gradually rose to 130/70 mmHg. She was fully conscious and was transferred to the sub-intensive care unit (ICU), with vital monitoring undertaken for 36 h. Five h after the initial event, we checked her complete blood cell count (CBC), immunoglobulin E (IgE), and D-dimer concentrations. The CBC and IgE levels were within normal ranges, but the D-dimer level rose to 4.35 nmol/L (normal range: 0-0.5 nmol/L). She recovered without any complications, and was discharged from the sub-ICU ward 48 h after the initial event. A skin prick test was not performed due to the patient’s refusal.

DISCUSSION

Sugammadex was introduced in 2008, and is widely used in the European Union. It is known to be safe, particularly in terms of cardiovascular stability, and has a shorter onset time compared to neostigmine or pyridostigmine. In Korea, the Ministry of Food and Drug Safety approved the use of sugammadex in 2012, based on the Sugammadex Hypersensitivity Study (Study P06042) [6].

The diagnosis of perioperative anaphylaxis is clinical, and is based upon the presence of characteristic signs and symptoms [7]. The World Allergy Organization guidelines indicate the clinical criteria for diagnosing anaphylaxis, which are sudden onset (minutes to several hours); skin and mucosal tissue involvement; at least one sudden respiratory distress symptom or sign; and a sudden reduction in blood pressure. Our case fulfilled these criteria [7], as evidenced by the acute onset of hypersensitive symptoms, with involvement of the skin, as well as hypotension.

Laboratory tests can help diagnose perioperative anaphylaxis as, typically, most anaphylactic reactions result from mast cell activation, which may be revealed by elevations in serum tryptase levels [7,8]. The currently available tryptase assay, however, is limited, and a basal level of serum tryptase is needed for the diagnosis of anaphylaxis, as patients with mastocytosis, decreased kidney function, or obesity show elevated baseline tryptase levels [9]. Moreover, the serum tryptase level is not elevated in basophil-induced anaphylaxis [9].

D-dimer testing is useful in excluding pulmonary embolism in patients when used with assessment of clinical probability. However, it has poor specificity and is elevated in a variety of settings, including anaphylaxis, due to activation of the coagulation pathway by allergic mechanisms [10].

Blood testing for specific IgE can be useful to confirm milk, egg, peanut, tree nut and fish allergies. But laboratory IgE evaluations for most medications are unavailable [11] and the count of white blood cells was not a big change.

Skin tests remain the gold standard for the detection of IgE-mediated reactions, and involve exposing the mast cells of the patients’ skin to the allergen suspected of causing the anaphylaxis. In our case, we proposed a free skin test and stressed its importance, but even several weeks after the incident, the patient refused. In previous reports, either skin-prick tests or intradermal tests have been performed to detect hypersensitivity to sugammadex [8]. However, there are no established guidelines with respect to skin testing for hypersensitivity to sugammadex [12]. A recent study showed that low-dose (<1/500) intradermal tests did not cause skin irritation and high-dose (>1/100) intradermal tests produced false-positive reactions [12]. However, it is difficult to exclude the possibility of false-positive reactions, as well as the possibility of inducing another anaphylactic shock reaction during the intradermal test. Thus, skin test guidelines need to be developed.

Sugammadex-induced anaphylactic shock generally develops post-operatively in patients who receive general anesthesia. Godai et al. [13] reported 3 cases of suspected sugammadex-induced anaphylaxis; all cases developed 3 to 4 minutes after administration of sugammadex. Takazawa et al. [14] also reported cases of suspected anaphylaxis caused by sugammadex, all of which developed 1 to 3 min after sugammadex administration. These time points, when the patient is already extubated and transferred to the recovery or intensive care unit, are typically less monitored. Therefore, early diagnosis, monitoring, and
treatment are required. In the present case, the patient was treated with a large amount of crystalloid, 100 mg of hydrocortisone, 10 mg of ephedrine, and a phenylephrine bolus and intravenous infusion. Epinephrine is the first-choice treatment for anaphylaxis, and is more powerful than ephedrine, but can also cause more complications. For our patient, we planned to treat her with epinephrine if her BP level did not rise after ephedrine treatment. Fortunately, her BP level improved after treatment with ephedrine and phenylephrine. In the case of the other papers, the patient with anaphylactic shock was treated with only ephedrine and phenylephrine [15].

In summary, the prevalence of anaphylactic shock caused by sugammadex is low, but it is severe and occurs within minutes of administration. Therefore, sugammadex should be administered carefully, and requires careful patient monitoring in the operating room for at least 5 min, until the patients are transferred to recovery or intensive care. There is no definite diagnostic tool for sugammadex-induced anaphylactic shock, but the present case meets the clinical criteria for anaphylactic shock, and represents the first suspected case of this condition in Korea. It indicates that more studies regarding sugammadex hypersensitivity detection tools are required.

REFERENCES