



Case Report

Successful management of rocuronium-induced anaphylactic reactions with sugammadex: a case report^{☆,☆☆}

Takashi Kawano MD, PhD (Associate Professor)*, Takahiko Tamura MD (Resident), Mayuko Hamaguchi MD (Resident), Tomoaki Yatabe MD (Assistant Professor), Koichi Yamashita MD, PhD (Associate Professor), Masataka Yokoyama MD, PhD (Professor)

Department of Anesthesiology and Critical Care Medicine, Kochi Medical School, Kochi, 783-8505, Japan

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Abstract Sugammadex, a new reversal agent for rocuronium, encapsulates the rocuronium molecule and results in rapid reversal of rocuronium-induced neuromuscular blockade. A case in which sugammadex was used to treat an anaphylactic reaction that occurred after rocuronium is presented. The binding/encapsulation of rocuronium by sugammadex may selectively eliminate the antigenic quaternary ammonium activity of circulating rocuronium, and prevent the propagation of rocuronium-induced anaphylaxis.

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1. Introduction

Anaphylactic reactions during anesthesia are rare intra-operative events that may be fatal [1–2]. The most frequent pharmacologic cause of perioperative anaphylaxis is the muscle relaxant [1,2], and their common allergenic epitope is the quaternary ammonium (QA) ion, which is responsible for the neuromuscular blocking effects of these drugs [1–3].

Sugammadex selectively encapsulates rocuronium molecules and rapidly reverses rocuronium-induced neuromuscular blockade [4]. This unique pharmacological characteristic of sugammadex suggests that it may be effective against rocuronium-induced anaphylaxis [5]. McDonnell et al reported the first clinical case of the successful management of rocuronium-induced severe anaphylaxis with sugammadex [6]. Our case report supports the effectiveness of sugammadex against rocuronium-induced anaphylaxis.

2. Case report

A 62-year-old, 45 kg, 150 cm woman with carcinoma of the right breast was scheduled for modified radical mastectomy. Three weeks before the surgery, she underwent preoperative chemotherapy with trastuzumab and paclitaxel, and afterward she developed mild leukopenia, with a white

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* Correspondence and reprint requests: Takashi Kawano, MD, PhD, Department of Anesthesiology and Critical Care Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi, 783-8505, Japan. Tel.: 81 88-880-2471; Fax: 81 88-880-2475.

E-mail address: takashika@kochi-u.ac.jp (T. Kawano).

blood cell count of 2,900 cells/mm³. She had no history of surgery or food/drug allergies. None of the routine preoperative tests, including chest radiography and electrocardiography (ECG), showed any abnormalities.

On the day of the surgery, the patient received neither premedication nor preoperative antibiotics. Monitors included ECG, heart rate (HR), non-invasive blood pressure (BP), blood oxygen saturation (SpO₂), and end-tidal CO₂. Her preanesthetic vital signs were BP 116/62 mmHg, HR 47 bpm, and SpO₂ 99%. General anesthesia was induced with remifentanyl at 0.2 µg/kg/min and target-controlled infusion (TCI) of propofol at 3.0 µg/mL. At loss of eyelash reflex, vecuronium 20 mg was administered, and the trachea was intubated after a short period of facemask ventilation. Anesthesia was continued with propofol and remifentanyl, which were titrated to maintain a Bispectral Index of approximately 50.

Immediately after receiving rocuronium, the patient developed intense generalized urticarial erythema and moderate hypotension (systolic BP 65–80 mmHg) with HR varying between 70 and 90 bpm; however, bronchospasm did not occur. The clinical signs and their onset suggested a rocuronium-induced, grade II (Ring-Messmer severity scale [2]) anaphylactic reaction. In the 30-minute period after the rocuronium administration, the patient was treated with intravenous (IV) ephedrine 4 mg, a rapid infusion of Ringer's acetate solution, and Trendelenburg positioning. Her BP did not improve. As the patient did not develop profound hypotension, epinephrine was not administered.

Her skin symptoms tended to spread from the trunk to the head, neck, limbs, and mouth. We considered the possibility of progressive worsening of the anaphylactic reaction. A bolus of IV sugammadex 200 mg was administered to remove the circulating antigen. Shortly afterward, the patient's skin symptoms fully resolved and the hypotension was spontaneously restored to the preinduction level. The planned operation was performed. No additional dose of muscle relaxant was administered thereafter. Although anesthesia was maintained with TCI propofol and continuous infusion of remifentanyl, no anaphylactic reactions were observed. The operation was completed one hour and 50 minutes later, without further complications. Tracheal extubation was performed in the operating room. The patient's postoperative recovery course was unremarkable.

On the first day after the operation, we informed the patient that an anaphylactic reaction had occurred during anesthesia and explained the risk of its recurrence during subsequent anesthesia. Unfortunately, she refused to undergo assessments, including prick or intradermal tests, for definitive diagnosis. She was discharged from the hospital on postoperative day 8.

3. Discussion

Muscle relaxants, including rocuronium, are the anesthetic drugs most commonly implicated in perioperative

anaphylaxis [1,2]. In the present case, the patient developed moderate grade II anaphylactic reactions after rocuronium administration, and the symptoms completely resolved after sugammadex administration. Therefore, this case supports the hypothesis that sugammadex has a novel therapeutic property of preventing the protraction and worsening of rocuronium-induced anaphylaxis.

Although the mechanism of muscle relaxant-induced anaphylaxis is not fully understood, studies have suggested that the substituted QA groups in this class of drugs are the main allergenic determinants that may interact with immunoglobulin E [3]. Sugammadex acts as a synthetic receptor by encapsulating the rocuronium molecule and promoting its dissociation from the nicotinic acetylcholine receptor [4]. In addition, the negatively charged side chains of sugammadex electrostatically interact with the QA group of rocuronium. Thus, one plausible mechanism is that formation of the rocuronium-sugammadex complex leads to the elimination of QA epitopes on rocuronium molecules from circulation.

To confirm this possibility, we conducted an additional *in vitro* experiment to test whether sugammadex affected the QA activity of rocuronium by using specific reagent strips as a QA indicator (Merkoquant 117920; Merck KGaA, Darmstadt, Germany). As shown in Fig. 1, reagent strips showed a positive reaction (green) with 50 µg/mL of rocuronium (Eslax; Schering-Plough, Tokyo, Japan). Pre-mixing of rocuronium at a concentration of 50 µg/mL with sugammadex (Bridion; Schering-Plough) at 38°C for 15 minutes partially antagonized (lighter green) the QA activity at 50 µg/mL and completely diminished (yellow) it at 250 µg/mL and greater. These results support the hypothesis that the antigenic activity of circulating rocuronium may be rapidly eliminated by formation of the rocuronium-sugammadex complex.

The patient in this case report showed moderate anaphylactic reactions without hemodynamic collapse (Grade II) after the administration of rocuronium. In such a circumstance, the circulating antigen should be withdrawn whenever possible to avoid the worsening of symptoms and

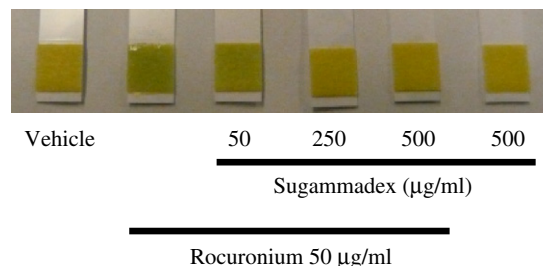


Fig. 1 Semi-quantitative measurement of quaternary ammonium (QA) activity of rocuronium by visual detection of the specific indicator. QA compounds react with an indicator, resulting in a change in the color of the test strips from yellow (no QA) to green. Vehicle (distilled water) and sugammadex alone show no reaction (yellow). The experiments were performed in triplicate, and the same pattern of reactions was observed.

to reduce the severity of symptoms [1]. Encapsulation of the antigenic rocuronium epitope by sugammadex may enable this ideal treatment. An earlier case report, by McDonnell et al [6], described the efficiency of sugammadex in treating rocuronium-induced severe anaphylactic reactions associated with cardiovascular collapse (Grade IV). These two case reports showed that sugammadex has a therapeutic effect on rocuronium-induced anaphylaxis irrespective of its severity, which may range from mild to severe and life-threatening.

Anaphylactic reactions during general anesthesia are often life-threatening [2]. Thus, early clinical diagnosis and immediate management are essential to prevent mortality and morbidity. Perioperative anaphylactic reactions are diagnosed on the basis of clinical features [1,2] such as the interval between the introduction of a causative agent and the onset of symptoms. In our case, the symptoms of anaphylaxis occurred immediately after IV rocuronium administration. These clinical signs suggested that rocuronium was the causative agent of the anaphylactic reaction. However, because anaphylaxis may occur at any time and may be caused by all potentially allergenic agents, precise identification of the drug may be difficult during the perioperative period.

The present case suggests that administration of sugammadex resulted in improvement of the anaphylactic symptoms that occurred after rocuronium administration. This response implicated rocuronium as the causative agent. A limitation of this case was the lack of direct biological and

immunological confirmation of rocuronium as the causative agent. Accordingly, we cannot conclusively rule out the possibility of anaphylaxis from other causes.

In conclusion, we report the successful use of sugammadex in the management of an anaphylactic reaction occurring after the administration of rocuronium for muscle relaxation. This finding suggests that the binding/encapsulation of rocuronium by sugammadex may cause rapid, selective elimination of circulating rocuronium antigenic activity.

References

- [1] Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009;111:1141-50.
- [2] Mertes PM, Laxenaire MC, Alla F; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. *Anesthesiology* 2003;99:536-45.
- [3] Ebo DG, Venemalm L, Bridts CH, et al. Immunoglobulin E antibodies to rocuronium: a new diagnostic tool. *Anesthesiology* 2007;107:253-9.
- [4] Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg* 2007;104:575-81.
- [5] Jones PM, Turkstra TP. Mitigation of rocuronium-induced anaphylaxis by sugammadex: the great unknown. *Anaesthesia* 2010;65:89-90.
- [6] McDonnell NJ, Pavy TJ, Green LK, Platt PR. Sugammadex in the management of rocuronium-induced anaphylaxis. *Br J Anaesth* 2011;106:199-201.