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Perioperative anaphylaxis caused by rocuronium bromide: a case series of four patients with skin test confirmation

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Dear Editors,

Perioperative anaphylaxis is a rare but life-threatening complication, occurring in approximately 1 in 10,000–20,000 anesthetic procedures. Prompt recognition of perioperative anaphylaxis is often challenging because patients are under general anesthesia and unable to communicate symptoms. Neuromuscular blocking agents are the most common triggers, with rocuronium bromide being the leading cause [1]. Here we report four cases of rocuronium bromide-induced anaphylactic shock encountered at our institution and summarize their clinical characteristics.

The clinical features of the four cases are summarized in Table 1. The patients ranged in age from 16 to 47 years, and two were female. Anaphylactic reactions occurred within 2–20 min after anesthesia induction. All patients developed hypotension accompanied by skin manifestations such as generalized erythema or wheals, except for one case in which only mild erythema appeared after the onset of circulatory collapse. Tryptase levels were elevated in both measured cases. Tryptase levels were measured 30 min, 2 h, and 48 h after symptom onset in two patients. In both cases, an increase of more than four times from baseline was observed. Serum tryptase measurement is useful in supporting the diagnosis of perioperative anaphylaxis. However, interpretation should be based not only on absolute values but also on changes from the individual baseline. Previous studies have suggested that even tryptase levels within the normal range may be clinically significant when increased from baseline, whereas elevated baseline levels alone do not necessarily indicate anaphylaxis [2].

Skin testing was conducted to identify the causative agent. In one patient, a skin prick test (at a maximum concentration: 10 mg/mL) performed 3 weeks after the event revealed a positive reaction to rocuronium bromide. In the other three patients, prick tests were negative, but intradermal tests (at a maximum concentration: 0.1 mg/mL) showed positive reactions to rocuronium bromide. Saline and histamine were used as negative and positive controls, respectively, and skin reactions were evaluated after 15–20 min. For the prick test, a positive reaction was defined as a wheal diameter of ≥3 mm or a wheal size greater than half that of the positive control. For the intradermal test, a positive reaction was defined as an erythema diameter of ≥20 mm or a wheal diameter of ≥9 mm.

Tests for other suspected anesthetic agents were negative in all patients. Based on the clinical course and the results of skin testing, all four cases were diagnosed as rocuronium bromide-induced anaphylactic shock. The concentrations used for skin testing followed previously recommended non-irritating concentrations for neuromuscular blocking agents. Subsequent surgeries were successfully performed without the use of rocuronium.

Perioperative anaphylaxis is most commonly triggered by neuromuscular blocking agents, followed by latex and antibiotics [1]. Rocuronium has been reported to account for a

TABLE 1 Clinical characteristics and diagnostic findings of the four patients.

Age Sex	Onset time	Main symptoms	Tryptase concentration	Diagnosis	Anesthesia History
① 16-year-old, female	10 min	Hypotension, Tachycardia, Generalized erythema	Not performed	Skin prick test	None
② 22-year-old, male	10 min	Hypotension, Tachycardia, Generalized wheals	Elevated	Intradermal test	Yes Rocuronium (6 times)
③ 27-year-old, female	2 min	Generalized erythema, Hypotension, Facial edema	Elevated	Intradermal test	None
④ 47-year-old, male	20 min	Hypotension, Tachycardia, Desaturation, Anterior chest erythema	Not performed	Intradermal test	None

substantial proportion of such reactions. Cross-reactivity among neuromuscular blocking agents is also well recognized. Previous studies have reported positive skin test reactions to vecuronium in approximately 40% and to suxamethonium in approximately 44% of patients with rocuronium allergy [3].

Skin testing is an important diagnostic tool for perioperative anaphylaxis, but appropriate test concentrations must be used to avoid false-positive reactions due to the pharmacological histamine-releasing properties of neuromuscular blocking agents. Current recommendations suggest performing skin tests at least 4–6 weeks after anaphylaxis because early testing may result in false-negative findings due to temporary depletion of mast cell mediators. However, early skin testing may be clinically useful when urgent reoperation is required, particularly in patients with malignant disease or when delays in surgery may adversely affect prognosis. In our series, one patient underwent skin testing 3 weeks after the anaphylactic event and showed a positive reaction on the prick test. Therefore, the timing of testing should be determined according to the clinical context [4].

Two mechanisms have been proposed for rocuronium-induced anaphylaxis: IgE-mediated or non-IgE-mediated pathways. IgE-mediated reactions are thought to be related to sensitization against the quaternary ammonium structure shared by many neuromuscular blocking agents. This structure is widely present in daily products such as cosmetics, detergents, and disinfectants, and sensitization through environmental exposure may explain why anaphylaxis sometimes occurs in patients without documented prior exposure to rocuronium. Notably, several patients developed anaphylaxis despite no documented history of prior exposure to rocuronium. This finding supports the hypothesis that prior sensitization to quaternary ammonium structures through environmental exposure may play a role in the development of anaphylaxis.

In contrast, non-IgE-mediated reactions may occur through direct activation of mast cells. Rocuronium has been identified as an agonist of the Mas-related G protein-coupled receptor X2 (MRGPRX2), which can induce mast-cell degranulation independent of IgE. Such reactions may present predominantly with cardiovascular symptoms and may be accompanied by minimal or delayed skin manifestations [5]. In one of our cases (Case 4), hypotension preceded the appearance of cutaneous symptoms, and the skin manifestations were mild. Although the mechanism could not be confirmed, the clinical presentation in Case 4 may be compatible with previously reported MRGPRX2-mediated reactions. Notably, cutaneous symptoms may be absent or subtle in perioperative anaphylaxis, which may delay recognition during anesthesia. In such situations, prompt intervention is essential. In all cases, prompt treatment was initiated immediately after the onset of anaphylaxis. Management included discontinuation of suspected agents, administration of vasopressors, intravenous fluids, and, when necessary, epinephrine. Early recognition and rapid intervention were critical for hemodynamic stabilization in all patients. These findings underscore the importance of close intraoperative monitoring and preparedness for immediate treatment of anaphylaxis.

In conclusion, we experienced four cases of perioperative anaphylactic shock caused by rocuronium bromide. These cases highlight the importance of early recognition of perioperative anaphylaxis and careful evaluation using appropriately timed skin testing. Awareness of both IgE-mediated and non-IgE-mediated mechanisms may help clinicians better understand the diverse clinical presentations of rocuronium-induced anaphylaxis. Clinicians should be aware that perioperative anaphylaxis may occur even in patients with no documented prior exposure to rocuronium and may present without prominent cutaneous findings. In addition, careful selection of alternative neuromuscular blocking agents and avoidance of cross-reactive drugs are essential for safe subsequent anesthesia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for

the publication of any potentially identifiable images or data included in this article.

Author contributions

SA collected the clinical data and drafted the initial manuscript. NY performed the skin testing for diagnostic confirmation and contributed to the critical revision of the manuscript. RW supervised the entire study and provided final approval for the version to be published. All authors contributed to the article and approved the submitted version.

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