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BRIEF REPORT

Incidence of Anaphylaxis Associated With Sugammadex

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We retrospectively investigated the incidence of potential sugammadex-induced anaphylaxis at a single center in Japan over a period of 3 years. The overall incidence of intraoperative hypersensitivity reaction was 0.22% (95% confidence interval [CI], 0.17%–0.29%), and the incidence of anaphylaxis was 0.059% (95% CI, 0.032%–0.10%). The total number of patients who received sugammadex during the study period was 15,479, and the incidence of anaphylaxis associated with sugammadex was 0.039% (n = 6; 95% CI, 0.014%–0.084%). This result implies that the incidence of sugammadex-associated anaphylaxis could be as high as that for succinylcholine or rocuronium. A prospective study, including testing for identification of cause, is necessary to confirm the exact incidence of sugammadex-induced anaphylaxis; however, the present finding calls attention to this potential. (Anesth Analg 2018;126:1505–8)

Anaphylaxis is defined as a life-threatening hypersensitivity reaction with systemic allergic symptoms; it occurs rarely during surgery and anesthesia. Neuromuscular blocking agents and antibiotics are considered common causes of anaphylaxis.[1] When symptoms associated with histamine reaction, such as skin rash, hypotension, tachycardia, and wheezing, appear suddenly after injection of these agents, anaphylaxis is suspected, and treatment should be initiated immediately. As far as is possible, it is essential to know the risk of anaphylaxis for these types of agents.

Sugammadex, a reversal agent for rocuronium and vecuronium, is available for clinical use in many countries. Whereas it has advantages over anticholinesterases, such as faster recovery from neuromuscular blockade and lesser incidence of residual paralysis,[2,3] there are concerns regarding allergy and anticoagulation.[4,5] A number of cases of hypersensitivity reaction in response to sugammadex have been reported,[6] but the incidence of anaphylaxis has not been sufficiently elucidated. Since the first use of sugammadex in Japan in 2010, the Japanese Society of Anesthesiologists has reported an incidence of sugammadex-associated anaphylaxis of 0.0029%,[4] based on estimates from the manufacturer. However, given the calculation method, the incidence is likely underestimated and remains unclear.

Our surgical center has not stored anticholinesterases since December 2014, and sugammadex has been commonly administered to reverse neuromuscular blockade. In the present study, we retrospectively investigated the incidence of anaphylaxis potentially caused by sugammadex at a single center in Japan over a period of 3 years. The primary outcome was the incidence of sugammadex-associated anaphylaxis, essential information for patient safety.

METHODS

This study was approved by the ethics committee of Jikei University School of Medicine (Tokyo, Japan) in November 2015. A retrospective investigation was performed using the databases documenting anesthetic management and perioperative events at the Department of Anesthesiology, Jikei University School of Medicine.

All surgical cases attended by anesthesiologists from September 2012 to August 2015 were evaluated. In each case, an attending anesthesiologist qualified by the Japanese Society of Anesthesiologists completed and submitted an assessment form of perioperative events, including hypersensitivity reactions and other adverse events related to circulation, respiration, the central or peripheral nervous system, airway, catheter insertion, depth of anesthesia, etc. All assessment forms of perioperative events during the study period were reviewed, and cases of intraoperative hypersensitivity reactions were identified in light of the anesthetic records and the free-text comments on the form. Applicable clinical signs of intraoperative hypersensitivity reactions include erythema, urticaria, hypotension, tachycardia, dyspnea, bronchospasm, etc, which were described in the clinical severity scale of immediate hypersensitivity reactions adapted from Ring and Messmer.[7,8] These were assessed to determine whether they corresponded to the definition of anaphylaxis according to the World Allergy Organization guidelines (Table 1).[9] Cases of potential sugammadex-associated anaphylaxis were examined further in terms of patient background (ie, allergy history, comorbidity of asthma, surgical history, and previous exposure to sugammadex), sugammadex dose, onset of reaction, clinical symptoms, treatments, time to achieve hemodynamic stability, diagnostic tests, and course.

The total number of patients who received sugammadex during the study period was determined, along

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with the incidence of potential sugammadex-associated anaphylaxis. We estimated that this proportion would be approximately 0.04%, and to have a 0.07% width in the 95% confidence interval (CI) of this estimate, 12,539 cases were required for this retrospective study. The 95% CIs for incidence were calculated using the Clopper–Pearson method.

RESULTS

The number of surgical cases attended by anesthesiologists during the study period was 23,608, and an assessment form of perioperative events was submitted for all cases. The overall incidence of intraoperative hypersensitivity reaction was 53 (0.22%; 95% CI, 0.17%–0.29%), and the incidence of anaphylaxis was 14 (0.059%; 95% CI, 0.032%–0.10%). The

Table 1. Clinical Criteria for Diagnosing Anaphylaxis Adapted From World Allergy Organization Guidelines[9]

Anaphylaxis was diagnosed when any of the following 3 criteria were fulfilled:

1. Acute onset of illness with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching, or flushing) and at least 1 of the following:
   - A. Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, or hypoxemia)
   - B. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia, syncope, or incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient:
   - A. Involvement of the skin-mucosal tissue (eg, generalized urticaria, itching, or flushing)
   - B. Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, or hypoxemia)
   - C. Reduced blood pressure or associated symptoms (eg, hypotonia, syncope, or incontinence)
   - D. Persistent gastrointestinal symptoms (eg, crampy abdominal pain or vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient:
   - A. Infants and children: low systolic blood pressure (age specific[a]) or >30% decrease in systolic blood pressure
   - B. Adults: systolic blood pressure of <90 mm Hg or >30% decrease from that patient's baseline

[a]Low systolic blood pressure for children is defined as <70 mm Hg from 1 month to 1 year of age, <(70 + [2 × age]) mm Hg from 1 to 10 years of age, and <90 mm Hg from 11 to 17 years of age.

Table 2. Six Cases of Anaphylaxis That Occurred During Emergence From General Anesthesia

No.	Age (y)	Sex	Height (cm)	Weight (kg)	ASA Physical Status	Allergy History	Asthma	Surgical History	Previous Exposure to Sugammadex	Sugammadex Dose (mg)
1	63	F	151	48	II	Latex	No	Yes	Unidentified	100
2	60	F	157	54	I	No	No	Yes	No	120
3	29	F	160	49	IE	No	No	No	No	200
4	21	M	176	53	I	No	Yes	Yes	No	200
5	46	F	159	89	II	No	Yes	Yes	No	200
6	43	F	163	53	I	No	No	No	No	200

(*Continued*)

total number of patients who received sugammadex during the study period was 15,479, and the incidence of anaphylaxis potentially caused by sugammadex was 6 (0.039%; 95% CI, 0.014%–0.084%).

The details of 6 cases of potential sugammadex-associated anaphylaxis are summarized in Table 2. After achieving hemodynamic stability with treatment for anaphylaxis, 1 patient was transferred to the intensive care unit for overnight observation and was administered a single dose of hydrocortisone (200 mg). The 5 others were moved to the general ward after observation in the postanesthesia care unit, and received no additional medication. All patients who experienced anaphylaxis potentially caused by sugammadex recovered with no major problems, including no biphasic reaction.

DISCUSSION

This retrospective, single-center study was undertaken to elucidate the incidence of anaphylaxis associated with sugammadex. The total number of patients who received sugammadex during the study period was 15,479, and the incidence of anaphylaxis potentially caused by sugammadex was 0.039% (6/15,479; 95% CI, 0.014%–0.084%). Although the cause of anaphylaxis was not specifically identified in this study, the clinical observations were that symptoms corresponding to anaphylaxis developed soon after injection of sugammadex.

Neuromuscular blocking agents are considered a common cause of anaphylaxis. A recent study reported that the incidence of anaphylaxis caused by succinylcholine, rocuronium, and atracurium is 0.048% (95% CI, 0.025%–0.084%), 0.04% (95% CI, 0.015%–0.087%), and 0.0045% (95% CI, 0.00092%–0.013%), respectively.[10] Differences in study design should be considered, but the results of the present study imply that the incidence of sugammadex-induced anaphylaxis might be as high as that of succinylcholine- or rocuronium-induced anaphylaxis.

According to a report published by the Japanese Society of Anesthesiologists in 2013, which was based on investigation by the manufacturer, the incidence of sugammadex-associated anaphylaxis was 0.0029%;[4] our present result of 0.039% is approximately 13 times this value. We used the same definition of anaphylaxis as the manufacturer, which does not specify tests, such as skin test, to identify the cause. Whereas the reason for the apparent difference is likely multifactorial, a possible reason for the discrepancy may be the

Table 2. Continued

Time From Injection of Sugammadex to Onset of Reaction (min)	Symptoms	Treatment	Time to Achieve Hemodynamic Stability (min)[a]	Diagnostic Tests
≤1	Hypotension: 43/20 mm Hg Tachycardia: 126 bpm Decreased Spo_2: 79% Elevated airway pressure: 46.8 cm H_2O	Phenylephrine: 0.2 mg IV × 2 Epinephrine: 10–40 μg IV × 5 Chlorpheniramine: 10 mg IV Famotidine: 20 mg IV Hydrocortisone: 100 mg IV	12	Serum tryptase:[b] 27.7 μg/L at the time of reaction; 8.7 μg/L the following day DLST for sugammadex: negative
2	Hypotension: 43/23 mm Hg Tachycardia: 118 bpm Generalized erythema Facial and cervical edema	Phenylephrine: 0.1–0.2 mg IV × 4 Epinephrine: 10–40 μg IV × 4 Hydrocortisone: 200 mg IV	15	None
2	Hypotension: 43/21 mm Hg Tachycardia: 128 bpm Trunk and upper limb urticaria	Epinephrine: 10 μg IV and 0.3 mg IM Chlorpheniramine: 10 mg IV Famotidine: 20 mg IV Hydrocortisone: 100 mg IV	9	None
1	Hypotension: 47/18 mm Hg Tachycardia: 128 bpm Decreased Spo_2: 92% Elevated airway pressure: 45.2 cm H_2O Truncal erythema	Epinephrine: 100 μg IV × 2 Albuterol: 3 puffs Hydrocortisone: 100 mg IV	30	None
4	Hypotension: 48/33 mm Hg Tachycardia: increased from 65 to 109 bpm Decreased Spo_2: decreased from 100% to 95%	Phenylephrine: 0.1 mg IV Epinephrine: 10 μg IV × 2 Chlorpheniramine: 10 mg IV Famotidine: 20 mg IV	9	None
≤1	Hypotension: decreased from 140/70 to 70/39 mm Hg Tachycardia: 126 bpm Truncal erythema	Phenylephrine: 0.1 mg IV Famotidine: 20 mg IV Hydrocortisone: 200 mg IV	4	None

Abbreviations: ASA, American Society of Anesthesiologists; bpm, beats per minute; DLST, drug-induced lymphocyte stimulation test; F, female; IM, intramuscular injection; IV, intravenous injection; M, male; Spo_2, peripheral oxygen saturation.

[a]Hemodynamic stability was defined as maintaining systolic blood pressure above 90 mm Hg without treatment.

[b]Normal values for serum tryptase are 1–15 μg/L.

reporting system for adverse events. In the present study, the perioperative hypersensitivity reactions were reported in all cases with a specific assessment form of perioperative events. In contrast, the data from the manufacturer were based on voluntary reporting. It is very likely that voluntary reporting recognized only a subset of cases of sugammadex-associated anaphylaxis. In addition, population parameters were different. Whereas the parameter in the present study was an actual number based on the total number of patients who received sugammadex, the parameter reported by the manufacturer was estimated cases based on the number of shipments to be distributed. Thus, an amount of unused sugammadex might be included in the population parameter.

Diagnostic tests to indicate that anaphylaxis occurred in response to sugammadex were performed for only 1 case in the present study. The patient showed a positive response with respect to serum tryptase and a negative response to a drug-induced lymphocyte stimulation test, an in vitro test to identify the causative agent of hypersensitivity reactions. Nonetheless, the result cannot rule out sugammadex as the cause of anaphylaxis because the sensitivity of the drug-induced lymphocyte stimulation test is low.[11] Although the definitive diagnosis could not be made without objective evidence from diagnostic tests, the 6 cases are suggestive of anaphylaxis caused by sugammadex because the clinical symptoms corresponding to anaphylaxis occurred within 1–4 minutes after injection of sugammadex at the emergence from anesthesia.

A prospective study, including testing for identification of cause of anaphylaxis, will be necessary to confirm the exact incidence of sugammadex-induced anaphylaxis. However, we conclude that the incidence (0.039%; 95% CI, 0.014%–0.084%) may be similar to that for succinylcholine or rocuronium, and it is important to be alert to this possibility.

DISCLOSURES

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