

Anaphylactic Reactions to Native and Light-Exposed Sugammadex Suggested by Basophil Activation Test: A Report of 2 Cases

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We describe 2 patients who developed anaphylactic shock after sugammadex administration during anesthesia. Both had no history of prior sugammadex administration. The serum tryptase concentrations were elevated after the allergic reaction. Basophil activation testing 1 month after the events was positive for sugammadex in 1 patient, and negative in the other. However, it was positive for light-exposed sugammadex solution in both patients, suggesting a possible allergic reaction to a denatured compound of sugammadex generated by light exposure of the sugammadex solution. (A&A Practice. XXX;XXX:00–00.)

Sugammadex (SGX) is a modified cyclodextrin, and its molecular structure contains 8 side chains on the main sugar ring. A number of SGX-induced allergic reactions have been reported.¹ The fact that all reported patients reacted on their first exposure to SGX suggests a cross-reaction between SGX and γ -cyclodextrin as the primary cause of SGX allergy.² γ -Cyclodextrins present in common daily necessities, such as cosmetics, pharmaceuticals, and food additives, are presumed to cause sensitization. We present 2 patients with anaphylactic reaction after SGX administration, one of whom demonstrated a positive basophil activation test (BAT) to a denatured compound derived from SGX after light exposure. The patients provided written permission for publication of the reports.

CASE DESCRIPTION

Patient 1

A 65-year-old man underwent a levator muscle shortening surgery for ptosis. He had hypertension, diabetes mellitus, dyslipidemia, and gout, with no history of allergy and surgery. General anesthesia was induced with propofol, fentanyl, and rocuronium bromide (ROC) and maintained with sevoflurane and remifentanyl after tracheal intubation. Piperacillin was administered before skin incision. After 3 uneventful hours of surgery, the anesthetics were discontinued, and 100 mg (1.2 mg/kg) of SGX was administered. Three minutes later, the patient was conscious and breathing regularly, and the trachea was extubated. Five minutes after extubation, the patient suddenly became unconscious, cyanotic, and severely hypotensive (systolic blood pressure, <50 mm Hg). Reintubation was immediately performed without the administration of any drug, and vasopressors (36 mg of ephedrine, 0.5 mg of phenylephrine, and 0.37 mg

of norepinephrine) were administered. Marked edema and erythema were observed on the face, lips, tongue, and trunk. The peak inspiratory pressure increased to 50 cm H₂O. Chlorphenamine and methylprednisolone were administered. Transesophageal echocardiography and bronchoscopy after resuscitation excluded cardiovascular and airway abnormalities. Several hours later, the patient's hemodynamics stabilized and the edema resolved. Serum tryptase activity and the plasma histamine concentration were markedly increased at 3 hours after the event (Table 1). The patient was discharged on the fourth postoperative day without any complications.

One month after the event, SGX, ROC, and an SGX–ROC complex were investigated using the lymphocyte transformation test (LTT) and BAT in accordance with previous reports.^{3–5} Considering the instability of SGX on light exposure, we exposed an additional SGX preparation to light. The SGX concentration was adjusted to 8 mg/1.9 mL with Roswell Park Memorial Institute medium. Then, the solution was spread out over a Petri dish and exposed to a standard hot cathode fluorescence lamp for 2 hours at room temperature. The light source and the temperature followed recommendations for the photostability test for new drugs. The light intensity was approximately 1000 lux, which corresponds to the average brightness in the operation room. ROC was mixed with native SGX or light-exposed SGX at a ratio of 1:4 on the basis of weight. All preparations tested negative in the LTT. Light-exposed SGX showed positive findings in BAT, while native SGX showed negative findings (Table 2).

Patient 2

A 29-year-old woman underwent brain tumor resection. With the exception of diplopia and a facial nerve disorder related to the tumor, she was healthy and had no history of allergy and surgery. After propofol induction and endotracheal intubation facilitated by ROC, general anesthesia was maintained with continuous intravenous infusions of propofol and remifentanyl. Induction of anesthesia and patient positioning were uneventful. ROC was reversed with 100 mg (2.4 mg/kg) of SGX at 45 minutes after induction for the purpose of monitoring motor-evoked potential. Within 5 minutes after SGX administration, severe

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Table 1. Blood Mediator Concentration After Allergic Reaction

Interval between onset of symptoms and blood sampling	Patient 1		Patient 2	
	3 h	24 h	2 h	24 h
Serum tryptase ($\mu\text{g/L}$)	82.6	5.9	4.8	Below the measurement limit
Plasma histamine (ng/mL)	1.27	0.86	3.44	0.68

Table 2. Results of LTT and BAT

	Patient 1		Patient 2	
	LTT	BAT	LTT	BAT
SGX	Negative	Negative	Negative	Positive (37.9%)
ROC	Negative	Negative	Negative	Negative
SGX + ROC	Negative	Negative	N/P	N/P
ex-SGX	Negative	Positive (17.6%)	Negative	Positive (33.2%)
ex-SGX + ROC	Negative	Positive (4.5%)	N/P	N/P

A value in parentheses shows proportion of reactive basophils. Samples were regarded as positive when $>4\%$ in BAT.

Abbreviations: BAT, basophil activation test; ex-SGX, light-exposed sugammadex; LTT, lymphocyte transformation test; N/P; not performed; ROC, rocuronium bromide; SGX, sugammadex.

hypotension (systolic blood pressure, 35 mm Hg), tachycardia (120 beats/min), and generalized erythema developed. Cyanosis and bronchospasm were not noticeable. Fluids, 20 mg of ephedrine, 1.2 mg of phenylephrine, and 0.04 mg of adrenaline were immediately administered intravenously, followed by the administration of dexamethasone, famotidine, and chlorphenamine. Hemodynamic instability and erythema completely resolved within 30 minutes. After a 1-hour observation period, surgery was initiated. Surgery, emergence from anesthesia, and tracheal extubation were uneventful.

Serum tryptase activity and plasma histamine concentration in a blood sample obtained 2 hours after the event were markedly elevated (Table 1). Similar to patient 1, allergy tests for SGX, ROC, light-exposed SGX, and propofol were performed 1 month later. All preparations tested negative in LTT. Native and light-exposed SGX showed positive findings in BAT, whereas ROC and propofol showed negative findings (Table 2). The combination of SGX and ROC was not examined because of an insufficient blood sample.

DISCUSSION

Anaphylaxis caused by SGX is a critical adverse event in the perioperative period. Timely resuscitation and accurate diagnosis are essential. Table 3 summarizes recent case reports. In 5 of the 10 patients reported, the tryptase assay was positive, indicating mastocyte and basophil activation. SGX is a modified γ -cyclodextrin with 8 carboxyl thioether side chains attached at the sixth carbon position of the cyclic dextrose units.⁶ The SGX prescribing information states that the vial should be protected from light, because light exposure accelerates the deletion of side extensions from cyclodextrin, resulting in increased contamination of other compounds. Vials that are not protected from light should

be used within 5 days. The detached side chain is considered to be too minimal to develop antigenicity. On the other hand, once SGX has lost some of its side chains, its structure resembles that of γ -cyclodextrin. It is conceivable that some patients show positive allergic reactions to γ -cyclodextrin and no reaction to native SGX. It was reported that a patient exhibited positive intradermal test reactions to SGX and γ -cyclodextrin, but not to α - and β -cyclodextrin, after an anaphylaxis following SGX administration.⁷ In 3 normal individuals, an intradermal test for γ -cyclodextrin was negative. The authors speculated that patients may become sensitized to cyclodextrins contained in foods and other products used in daily life.

In patient 1, BAT was positive for light-exposed SGX, and negative for native SGX. These findings suggest that exposure of SGX to light produces a substance similar to γ -cyclodextrin, which might have been the source antigen triggering the anaphylactic reaction. The patient might have possessed immunoglobulin E (IgE) which only reacted to a γ -cyclodextrin-like substance generated by light exposure of SGX, but not to native SGX. The findings for patient 2 suggested that the patient possessed IgE against SGX, although they do not indicate whether the patient had IgE against another compound derived after light exposure. In any case, the compound that resembles γ -cyclodextrin and triggers a reaction remains unclear. The commercially available SGX vial may already contain up to 7 mg/mL mono-OH derivative of SGX.⁶ With regard to light exposure, in our case, SGX was protected from light during storage in a dedicated black plastic bag, and it was administered 2 hours after preparation in a syringe. The denaturation of SGX could have been the result of a combination of light exposure outside the vial and dilution with different pH solutions.

Two publications reported allergic reactions to an SGX–ROC complex, but not to SGX or ROC alone.^{8,9} The authors suggested that molecular conformational changes after encapsulation may modify drug antigenicity. In patient 1, BAT was negative for the SGX–ROC combination, implying no relationship between the SGX–ROC complex and an allergic reaction. In patient 2, an SGX–ROC complex was not tested.

Skin testing is routinely used for the diagnosis of allergic reactions. Unfortunately, both patients refused such tests. BAT is increasingly used as an alternative method. Although a standard protocol for BAT is not completely established¹⁰ to date, several studies have shown a sensitivity of 54%–92% and a specificity of 93%–100% for the hypersensitivity testing against neuromuscular blocking drugs compared to skin testing.¹¹ The use of CD203c as a basophil activation marker and SGX concentrations of 0.1–100 $\mu\text{g/mL}$ have been reported previously.⁵ We also used CD203c. The SGX concentration of 0.8–12.8 $\mu\text{g/mL}$ was within the previously reported range and identical to the blood concentrations calculated on the basis of its distribution volume. Despite the absence of skin testing results, the high specificity and low false-positive rate of BAT tend to support our diagnosis. Furthermore, multiple positive results with different reagents corroborate our interpretation that solutions of light-exposed SGX with or without ROC will contain some amounts of denatured and native SGX.

Table 3. Reported Anaphylactic Reactions After 2015 With Confirmed Sugammadex or Related Compound as Allergen

Reference	Country	Age (y)	Sex	Weight (kg)	Dose (mg)		Previous Exposure		Laboratory Test for Anaphylaxis	Antigen Conformation	
					ROC	SGX	ROC	SGX		Positive Agent	Method
Takazawa et al ⁵	Japan	13	M	40	30	80	N/R	-	Not done	SGX	Skin prick BAT
Yamada et al ¹²	Japan	19	F	50	N/R	N/R	-	-	Not done	SGX ROC	Intradermal
Nakanishi et al ¹³	Japan	60	F	50	N/R	200	N/R	-	N/R	SGX	Skin prick
Yoo et al ¹⁴	Korea	35	M	109	90	200	-	-	Not done	SGX	Skin prick
Hotta et al ⁷	Japan	65	F	N/R	N/R	200	N/R	-	N/R	SGX	Intradermal
Ho et al ⁸	Australia	50	M	95	N/R	200	-	-	Tryptase(+)	γ-cyclodextrin SGX-ROC complex	Intradermal
Yamaoka et al ⁹	Japan	36	F	65	70	200	-	-	Histamine(-) Tryptase(+)	SGX-ROC complex	Skin prick
Ue et al ¹⁵	United Kingdom	50	M	N/R	N/R	200	N/R	-	Tryptase(+)	SGX	Skin prick Intradermal
		62	M	N/R	N/R	400	N/R	-	Tryptase(+)	SGX	Skin prick Intradermal
		63	M	N/R	N/R	100	N/R	-	Tryptase(+)	SGX	Intradermal

Abbreviations: BAT, basophil activation test; F, female; M, male; N/R, not reported; ROC, rocuronium bromide; SGX, sugammadex.

To our knowledge, this is the first report examining denatured SGX as a potential trigger of anaphylaxis. Although we are unable to define the exact role of light-exposed SGX, our findings suggest that an allergic reaction to SGX is not necessarily triggered by a single compound, and that a role of light exposure of SGX should be considered in allergen identification after an SGX-associated allergic reaction. Native SGX, denatured SGX, and a SGX-ROC complex seem to act as potential triggers. A multitude of triggering substances can be expected to be associated with a relatively high prevalence of allergic reactions to SGX and false-negative results when testing is restricted to native SGX. ■■

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DISCLOSURES

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REFERENCES

- Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. *Anaesthesia*. 2014;69:1251–1257.
- Menéndez-Ozcoidi L, Ortiz-Gómez JR, Olaguibel-Ribero JM, Salvador-Bravo MJ. Allergy to low dose sugammadex. *Anaesthesia*. 2011;66:217–219.
- McGowan EC, Saini S. Update on the performance and application of basophil activation tests. *Curr Allergy Asthma Rep*. 2013;13:101–109.
- Leysen J, Bridts CH, De Clerck LS, Ebo DG. Rocuronium-induced anaphylaxis is probably not mitigated by sugammadex: evidence from an in vitro experiment. *Anaesthesia*. 2011;66:526–527.
- Takazawa T, Horiuchi T, Yoshida N, Yokohama A, Saito S. Flow cytometric investigation of sugammadex-induced anaphylaxis. *Br J Anaesth*. 2015;114:858–859.
- The Center for Drug Evaluation and Research US FDA. BRIDION (sugammadex) Injection: Chemistry Review(s). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022225Orig1s000ChemR.pdf. Accessed October 20, 2017.
- Hotta E, Tamagawa-Mineoka R, Masuda K, et al. Anaphylaxis caused by γ-cyclodextrin in sugammadex. *Allergol Int*. 2016;65:356–358.
- Ho G, Clarke RC, Sadleir PH, Platt PR. The first case report of anaphylaxis caused by the inclusion complex of rocuronium and sugammadex. *A A Case Rep*. 2016;7:190–192.
- Yamaoka M, Deguchi M, Ninomiya K, Kurasako T, Matsumoto M. A suspected case of rocuronium-sugammadex complex-induced anaphylactic shock after cesarean section. *J Anesth*. 2017;31:148–151.
- Hoffmann HJ, Knol EF, Ferrer M, et al. Pros and cons of clinical basophil testing (BAT). *Curr Allergy Asthma Rep*. 2016;16:56.
- Leysen J, Sabato V, Verweij MM, et al. The basophil activation test in the diagnosis of immediate drug hypersensitivity. *Expert Rev Clin Immunol*. 2011;7:349–355.
- Yamada Y, Yamamoto T, Tanabe K, Fukuoka N, Takenaka M, Iida H. A case of anaphylaxis apparently induced by sugammadex and rocuronium in successive surgeries. *J Clin Anesth*. 2016;32:30–32.
- Nakanishi T, Ishida K, Utada K, Yamaguchi M, Matsumoto M. Anaphylaxis to sugammadex diagnosed by skin prick testing using both sugammadex and a sugammadex-rocuronium mixture. *Anaesth Intensive Care*. 2016;44:122–124.
- Yoo JH, Kim SI, Ok SY, et al. Suspected anaphylactic reaction associated with sugammadex: a case report. *Korean J Anesthesiol*. 2016;69:413–416.
- Ue KL, Kasternow B, Wagner A, Rutkowski R, Rutkowski K. Sugammadex: an emerging trigger of intraoperative anaphylaxis. *Ann Allergy Asthma Immunol*. 2016;117:714–716.