

CLINICAL INVESTIGATION

Comparison of incidence of anaphylaxis between sugammadex and neostigmine: a retrospective multicentre observational study

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Abstract

Background: Although cases of anaphylaxis caused by sugammadex have been reported, its incidence remains uncertain. Conversely, no studies have evaluated the incidence of anaphylaxis to neostigmine.

Methods: This was a retrospective multicentre observational study of patients who underwent surgery under general anaesthesia between 2012 and 2016 to compare the incidence of anaphylaxis with sugammadex with that of neostigmine at four tertiary hospitals in Japan. To ensure the quality of diagnosis, only cases with a clinical history suggestive of anaphylaxis, along with positive results from *in vitro* or *in vivo* testing, were assessed.

Results: From a total of 49 532 patients who received general anaesthesia included in this study, 18 cases of anaphylaxis were reported, of which six were attributable to sugammadex and none to neostigmine. There were no fatalities attributable to anaphylaxis. The incidence of anaphylaxis caused by all drugs or by sugammadex was calculated as 0.036% (95% confidence interval [CI]: 0.022–0.057%) and 0.02% (of the number of sugammadex cases) (95% CI: 0.007–0.044%), respectively.

Conclusions: The results suggest that neostigmine might be safer than sugammadex when assessing only the incidence of anaphylaxis. We believe that there is room for reconsideration of the choice of reversal agent for neuromuscular blocking agents by all anaesthetists.

Clinical trial registration: UMIN000022365; UMIN000033561.

Keywords: anaphylaxis; basophil activation test; neostigmine; neuromuscular blocking agents; skin tests; sugammadex

Editor's key points

- The incidence of anaphylaxis to sugammadex has not been well defined.
- A multicentre retrospective analysis of patients receiving general anaesthesia over a 4 yr period in Japan was performed to assess anaphylaxis to sugammadex and neostigmine.

- Of the 49 532 cases of general anaesthesia analysed, there were 18 cases of anaphylaxis (0.036%), including six reactions to sugammadex (0.02%) and none to neostigmine.
- The incidence of laboratory-confirmed anaphylaxis was higher for sugammadex than neostigmine, which must be considered along with other factors in the choice of reversal agents.

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Sugammadex is a synthetic cyclodextrin derivative that encapsulates amino-steroid neuromuscular blocking agents (NMBAs), especially rocuronium, to reverse their effect.¹ Sugammadex was developed to overcome the problems with neostigmine, including occasional incomplete reversal of neuromuscular block and the need for a concomitant use of an anticholinergic drug. Since the launch of sugammadex, several comparative studies between sugammadex and neostigmine have been conducted.^{2–5} A meta-analysis found the advantages of sugammadex vs neostigmine in terms of recovery time from both moderate and deep neuromuscular block.⁴ Moreover, there were significantly fewer composite adverse events with sugammadex compared with neostigmine, including bradycardia, postoperative nausea and vomiting, and overall signs of postoperative residual paralysis.⁴ Although this meta-analysis was based on large-scale data involving 4206 subjects from 41 studies, hypersensitivity reactions were not adequately evaluated. As the incidence of perioperative hypersensitivity is very low, at one case per thousand to tens of thousands,^{6,7} more extensive studies are needed to estimate the incidence of hypersensitivity to individual drugs, including sugammadex and neostigmine.

A significant number of cases of sugammadex-induced anaphylaxis have been reported.^{8,9} According to the post-marketing safety database, approximately 11.5 million patients in the USA had received sugammadex as of March 31, 2015. Based on 273 reported cases of anaphylaxis with 11.5 million doses, the incidence of anaphylaxis was estimated to be approximately 24 per 100 000 doses of sugammadex (0.024%), assuming that 10% of cases were reported.¹⁰ In a recent single-centre Japanese study, six cases of anaphylaxis were suspected to be caused by sugammadex during a 3 yr study period. This study estimated the incidence of sugammadex-induced anaphylaxis to be one in 2500 cases (0.039%) based on a study population of 15 479 patients.¹¹ In a 1 yr study of perioperative anaphylaxis in the UK, only one confirmed case of sugammadex anaphylaxis was reported from amongst an estimated 64 000 administrations (0.0016%).⁷ In contrast, the incidence of neostigmine-induced anaphylaxis is unknown, although there are few case reports of anaphylaxis attributable to neostigmine.^{12,13}

Whilst sugammadex appears to be used only in a limited number of cases in many countries because of its high cost, it is used routinely in Japan, and an estimated 10% of the population received sugammadex during an 8 yr period from 2010 to 2018.¹⁴ However, it is not clear how the use of sugammadex progressed in Japan during this period, and why the use of sugammadex is more frequent than in other countries.

In this study, we retrospectively investigated the incidence of perioperative anaphylaxis in Japan over a 5 yr period. To ensure the quality of diagnosis, only cases with a clinical history suggestive of anaphylaxis, along with positive results from *in vitro* or *in vivo* testing, were assessed.¹⁵ We compared the incidence of anaphylaxis caused by sugammadex and neostigmine directly, with the null hypothesis being that the incidence of anaphylaxis caused by sugammadex is higher than that by neostigmine. We also investigated changes in usage of sugammadex and neostigmine over time by obtaining sales data of these drugs over an 8 yr period, and we conducted an online survey of anaesthetists across Japan to determine the reasons for the popularity of sugammadex.

Methods

Subjects

This retrospective observational study conforms to the standards of the Declaration of Helsinki and was approved by the ethics committee of Gunma University Hospital. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (ID: 000022365; 000033561). This article adheres to Strengthening the Reporting of Observational Studies in Epidemiology guidelines. All consecutive cases of general anaesthesia in four Japanese hospitals (Gunma University Hospital, Isesaki Municipal Hospital, Japan Community Healthcare Organization, Gunma Chuo Hospital, and Gunma Saiseikai Maebashi Hospital) between January 2012 and December 2016 were included. As we aimed to collect data on anaphylaxis to all administered drugs, we also included cases where no NMBAs were used. We diagnosed anaphylaxis only when two or more of the following criteria were fulfilled: (i) evaluation using the clinical monitoring scoring system suggested the possibility of an immediate hypersensitivity reaction (net total score on the clinical grading scale ≥ 8)¹⁶; (ii) skin tests or basophil activation tests (BATs) showed a positive reaction to any of the drugs to which the patient was exposed during anaesthesia; and (iii) blood samples taken soon after the event showed an elevation in histamine or tryptase concentration. All participating hospitals used an electronic anaesthesia recording system, ensuring accuracy of all intra-anaesthesia clinical information, including all medications and substances administered before the episode of anaphylaxis, clinical features, and details of treatment. We obtained relevant patient information, including allergy history and past surgical history.

Use of neuromuscular blocking agents and their antagonists

We collected data on the use of NMBAs and their antagonists from all participating hospitals between January 2009 and December 2016. Data were extracted from the electronic anaesthesia information management system at each hospital. At hospitals where such a system was not available, the operators extracted data from paper-based anaesthesia charts. We purchased longitudinal medicine procurement data from IQVIA, Tokyo, Japan, to assess trends in the market share of NMBA antagonists throughout Japan between January 2009 and December 2016.

Skin and blood tests

Skin tests were performed in accordance with international guidelines.^{17–19} The recommended maximum drug concentration for skin prick tests (SPTs) for most drugs is an undiluted concentration, whilst that for intradermal tests (IDTs) is a 10-fold dilution.^{17,19} Bifurcated needles (Tokyo M.I. Co. Inc., Tokyo, Japan) were used for SPTs, which were considered positive when the size of the wheal increased by 3 mm or more in diameter after 20 min and was associated with a flare.¹⁹ IDTs were performed with 26-gauge needles (Terumo Co., Tokyo, Japan) to create a post-injection wheal of up to 4 mm in diameter, and were deemed positive when the diameter of the reactionary erythematous wheal was equal to at least twice

Table 1 Summary of the number of perioperative anaphylaxis events attributable to neuromuscular blocking agents and other drugs. CI, confidence interval; GA, general anaesthesia.

Hospital	Number of cases with GA	All cases of anaphylaxis				Caused by sugammadex				Caused by neostigmine			
		Number of cases each drug was used		Anaphylaxis Incidence (%)	95% CI (%)	Anaphylaxis Incidence (%)	95% CI (%)	Anaphylaxis Incidence (%)	95% CI (%)	Anaphylaxis Incidence (%)	95% CI (%)	Anaphylaxis Incidence (%)	95% CI (%)
		Sugammadex	Neostigmine										
A	23 358	12 149	1447	6	0.026	0.009	0.008	0	0.000	0	0.000	0	0.000
B	11 773	6912	1374	5	0.042	0.014	0.043	3	0.009	0	0.000	0	0.000
C	8112	5983	116	3	0.037	0.008	0.017	1	0.000	0	0.000	0	0.000
D	6289	4918	220	4	0.064	0.017	0.020	1	0.001	0	0.000	0	0.000
All	49 532	29 962	3157	18	0.036	0.022	0.020	6	0.007	0	0.000	0	0.000
						0.056			−0.046				
						−0.099			−0.127				
						−0.108			−0.093				
						−0.163			−0.113				
						0.022			−0.044				

that of the post-injection wheal after 20 min.¹⁹ In most cases, we performed SPTs first, and performed IDTs only when the SPTs showed negative reactions.^{18–20}

Optional blood tests to measure plasma histamine and serum tryptase concentrations were performed in most cases. The threshold concentration of histamine was set at 1 ng ml^{−1}. We determined that, when peak tryptase concentrations exceeded 1.2×baseline tryptase+2 µg L^{−1}, serum tryptase concentration was elevated.^{21,22} Blood samples were collected at the earliest opportunity after the start of reactions in the operating theatre. A baseline sample was also obtained 24 h after the reaction.

Basophil activation tests

The methods of the BATs are detailed elsewhere.^{23,24} Briefly, whole blood samples were obtained from patients with allergic reactions. BATs were performed using a flow cytometer (BD FACSCanto™ II Flow Cytometer; Japan BD Co., Tokyo, Japan). For detecting activated basophils, an Allergen kit (Beckman Coulter Inc., Tokyo, Japan) was used within 4 h after blood sampling. Blood samples were incubated with serial dilutions of culprit agents at 37°C. Anti-immunoglobulin (Ig)E-antibody and phosphate-buffered saline (PBS) were used as positive and negative controls, respectively. Samples were stained with 20 µl of a mixture containing anti-CRTH2-FITC, anti-CD203c-PE, and anti-CD3-PC7-conjugated antibodies (manufacture, location for antibodies). Basophils were selected based on a side scatter and low CD3−/CRTH2+ gate profile; at least 500 basophils were counted. The number of basophils with CD63 was counted in another set of samples. A maximum of 5% spontaneous expression of CD203c and CD63 after stimulation with the buffer solution (negative control) was accepted. The BAT was considered positive when the basophil stimulation index (drug/control) was ≥2, provided >5% drug-activated basophils were detected.^{25,26}

Online survey

An online survey was conducted to explore the use of reversal agents and the attitudes of 93 anaesthetists towards these agents. The survey was constructed and distributed using SurveyMonkey®, a commercially available online survey vehicle (<https://www.surveymonkey.com/>). The subjects were divided into two groups: Group A comprised 46 anaesthetists who had worked at the participating hospitals for at least 1 yr between January 2012 and December 2016. Group B comprised 47 anaesthetists who participated in the Japanese epidemiological study for perioperative anaphylaxis, which is an ongoing prospective multicentre observational study on perioperative anaphylaxis. Both groups were included, as we sought to survey not only anaesthetists at the participating hospitals, but also Japanese anaesthetists in general. The survey comprised four questions (Supplementary Table 1). The survey was available online for 1 month (August 2018 for Group A and September 2018 for Group B). Responses to Questions 3 and 4 were scored using a scale: the first item had a score of 5 points, the second 4 points, the third 3 points, the fourth 2 points, and the fifth 1 point.

Statistical analysis

The incidence of anaphylaxis was calculated as the fraction of the number of confirmed cases of anaphylaxis to the number

Table 2 Clinical background, anaphylactic symptoms, and blood test results in patients with anaphylaxis attributable to sugammadex. All patients had a clinical score of 8 or above, suggesting possible anaphylaxis.¹⁶ Anaphylactic symptoms appeared after sugammadex 80 mg administration in Case 3 and sugammadex 200 mg in other cases. A past history of drug allergies was present only in Case 4, an allergy to contrast media. AP, airway pressure; F, female; M, male; UI, unidentified.

Case	Age (yr)	Sex	Height (cm)	Weight (kg)	ASA physical status	Previous surgical history	Previous exposure to sugammadex	Onset of reaction (min)	Symptoms	Clinical score	Time to achieve haemodynamic stability (min)	Histamine (ng ml ⁻¹)		Tryptase (µg L ⁻¹)	
												Peak	Baseline	Peak	Baseline
1	75	F	152	71	2	Yes	No	3	BP: 40/undetectable mm Hg HR: 120 beats min ⁻¹ Thoracic erythema	25	15	—	—	—	—
2	34	M	159	62	1	No	No	1	BP: 70/40 mm Hg Generalised erythema	19	4	—	—	—	—
3	13	M	159	40	1	No	No	5	BP: unmeasurable HR: 160 beats min ⁻¹ Facial swelling Elevated AP	30	20	—	—	—	—
4	65	M	168	65	2	Yes	Yes	<1	BP: 40/25 mm Hg Generalised erythema Elevated AP	27	20	124.0	0.9	13.9	1.9
5	39	M	164	73	2	Yes	No	8	BP: 75/35 mm Hg HR: 130 beats min ⁻¹ Thoracic erythema	17	11	49.3	1.1	22.0	2.8
6	62	M	159	57	1	UI	UI	3	BP: 45/20 mm Hg Nausea	13	19	7.0	0.3	104.0	5.8

Table 3 Results of skin tests and basophil activation tests in patients with anaphylaxis after sugammadex administration. Numerical values in the SPT and IDT columns indicate the concentration of sugammadex that resulted in positive skin reactions. A concentration of 100 mg ml⁻¹ of sugammadex represents the undiluted/full-strength solution. The concentration of sugammadex and the proportion of activated basophils when basophils were most highly activated are shown in CD203c and CD63 columns. The percentage of activated basophils was obtained by subtracting 5%, which is the value activated by the negative control. Assessment of the BAT was performed based on the threshold we determined in our previous study.²³ BAT, basophil activation test; IDT, intradermal test; ND, no data; SPT, skin prick test.

Case	Skin tests			Basophil activation tests					
	SPT (mg ml ⁻¹)	IDT (mg ml ⁻¹)	Delay in skin tests (days)	CD203c		CD63		Result of BATs	Delay in BATs (months)
				Sugammadex concentration (mg ml ⁻¹)	Activated basophils (%)	Sugammadex concentration (mg ml ⁻¹)	Activated basophils (%)		
1	ND	1	31	10	49.3	1	26.3	Positive	35
2	ND	0.1	57	—	—	—	—	ND	—
3	1	ND	49	10	56.4	10	40.5	Positive	33
4	Negative	0.1	63	10	6.1	10	5.5	Positive	11
5	Negative	0.1	59	1	4.3	0.1	3.7	Positive	2
6	1	ND	28	1	42.6	1	25.3	Positive	3

of general anaesthesia cases. The 95% confidence interval (CI) for incidence was calculated by the Clopper–Pearson method using Sigma Plot 14.0 software (Systat Software Inc., San Jose, CA, USA).

Results

A total of 49 532 cases of general anaesthesia were included in this study. The number of cases involving reversal agents and that developed anaphylaxis are shown in Table 1. During the study period, 23 suspected cases of anaphylaxis occurred, of which 18 cases were confirmed as anaphylaxis (Grade 2: six cases; Grade 3: 10 cases; Grade 4: two cases), six of which were in response to sugammadex (Grade 2: two cases; Grade 3: four cases) and none to neostigmine (Supplementary Fig. 1). The total number of patients who received sugammadex during the study period was 29 962, and the incidence of sugammadex-induced anaphylaxis was six. The incidence of anaphylaxis caused by all drugs or by sugammadex was calculated as 0.036% (95% CI: 0.022–0.057%) and 0.02% (95% CI: 0.007–0.044%), respectively (Table 1).

The details of sugammadex-induced anaphylaxis cases are summarised in Tables 2 and 3. All patients met the diagnostic criteria of anaphylaxis, and they showed sufficient symptoms to suspect anaphylaxis after exposure to sugammadex with positive reactions in skin tests to sugammadex. Although the timing of blood sampling in the operating theatre varied from 10 to 90 min after the episode, both histamine and tryptase concentrations were increased in all three patients tested. The baseline concentrations of these substances in these patients were below the threshold. Although four patients required treatment with epinephrine, all patients recovered with no major problems, including a biphasic reaction. All patients showed positive reactions to sugammadex either in SPTs or IDTs performed 4–9 weeks after the episode. BATs showed positive reactions to sugammadex in all five patients tested. These results suggested that sugammadex was the likely causative agent of anaphylaxis in all six cases.

Information on the patients who developed anaphylaxis to agents other than sugammadex is shown in Tables 4 and 5. As in the patients with sugammadex-induced anaphylaxis, all 12 patients met the diagnostic criteria of anaphylaxis.

To examine the background factors related to anaphylaxis caused by sugammadex, we investigated the use of NMBA in participating hospitals. The total number of patients who received NMBA during the study period was 46 687, of whom 44 692 (95.7%) received rocuronium (Table 6). The number of patients who received antagonists to NMBA during the study period was 33 119, of whom 29 962 (90.5%) received sugammadex (Table 6).

The chronological changes in the use of antagonists to NMBA at participating hospitals are shown in Supplementary Figure 2a. Even though sugammadex was launched in Japan in April 2010, its average rate of use had already reached nearly 80% in 2011. The transition of NMBA antagonist usage at participating hospitals and the transition of total sales throughout Japan are shown in Supplementary Figure 2b for sugammadex and Supplementary Figure 2c for neostigmine. The number of cases using sugammadex increased dramatically, and those using neostigmine decreased during the study period. This trend was consistent with the sales data of both drugs.

The response rate of the online survey was 97.8%, as 91 out of 93 anaesthetists answered the questionnaire. The median duration of experience in clinical anaesthesiology practice amongst the respondents was 18 yr. There were no significant differences in the background characteristics of anaesthetists or their responses to the survey between the two groups. Therefore, the results of the questionnaire are described by adding the results of the two groups. For Question 1, 97.8% (89/91) of responders answered that they use sugammadex as they wish. For Question 2, the average of sugammadex use was 90.6 (17.7)%. The results for Questions 3 and 4 are summarised in Supplementary Figures 3a and b, respectively. The top three reasons for choosing sugammadex were certainty, rapidity, and safety of NMBA antagonism, whilst the main reasons for not choosing sugammadex were concerns about adverse effects, followed by cost or cost–benefit concerns.

Table 4 Clinical background, anaphylactic symptoms, and blood test results in patients with anaphylaxis induced by drugs other than sugammadex. All patients had a clinical score of 8 or more, suggesting possible anaphylaxis.¹⁶ A past history of drug allergies to ciprofloxacin was seen in Case 6 and to tropicamide in Case 8. AP, airway pressure; F, female; M, male; VF, ventricular fibrillation.

Case	Age (yr)	Sex	Height (cm)	Weight (kg)	ASA physical status	Surgical history	Culprit drugs	Onset of reaction (min)	Symptoms	Clinical score	Time to achieve haemodynamic stability (min)	Histamine (ng ml ⁻¹)		Tryptase (µg L ⁻¹)	
												Peak	Baseline	Peak	Baseline
1	61	F	147	44	1	Yes	Propofol	<1	Thoracic erythema Oral swelling Elevated AP	17	—	1.0	0.9	1.0	1.1
2	54	M	171	79	2	Unknown	Lidocaine	<1	BP: 44/37 mm Hg Wheal and erythema at epidural catheter insertion site	12	10	1.5	1.2	7.9	7.0
3	41	F	152	62	2	Yes	Rocuronium	<1	BP: 41/23 mm Hg HR: 170 beats min ⁻¹ Elevated AP Decrease in SpO ₂ to 82%	35	30	34.9	0.9	35.3	3.9
4	71	F	149	53	2	No	Cefazolin	10	BP: 40/18 mm Hg Generalised wheal and erythema	21	5	11.0	0.8	13.2	2.9
5	26	F	168	56	2	No	Cefazolin	2	BP: 34/21 mm Hg HR: 133 beats min ⁻¹ Unmeasured SpO ₂	26	26	115.0	1.0	17.7	2.5
6	83	F	157	59	2	Yes	Unidentified	Unknown	BP: 40/25 mm Hg HR: 125 beats min ⁻¹ Elevated AP to 25 cm H ₂ O	16	80	11.3	0.7	19.5	3.9
7	56	M	179	83	2	Yes	Cefoperazone 5 — sulbactam	5	VF Elevated AP	32	35	1.7	1.3	31.9	3.6
8	67	F	160	48	2	No	Cefazolin	3	BP: 60/45 mm Hg HR: 120 beats min ⁻¹ Generalised erythema	21	30	9.6	0.9	2.4	1.2
9	78	F	155	50	2	Unknown	Rocuronium	10	BP: 65/37 mm Hg Elevated AP Generalised erythema	19	5	0.8	0.7	2.9	1.8
10	21	M	180	67	1	Yes	Flurbiprofen	10	BP: 64/32 mm Hg HR: 120 beats min ⁻¹ Generalised erythema and itching	20	30	54.0	0.8	7.3	2.8
11	7	F	132	28	2	No	Cefazolin	10	BP: 40/22 mm Hg HR: 140 beats min ⁻¹ Decreased SpO ₂ to 80%	22	75	49.2	0.4	12.0	3.6
12	33	F	156	48	1	Unknown	Cefazolin	20	BP: 48/32 mm Hg HR: 140 beats min ⁻¹ Erythema at right upper limb	12	15	49.1	0.1	5.0	3.6

Table 5 Results of skin tests and basophil activation tests in subjects with anaphylaxis to drugs other than neuromuscular blocking agent antagonists. Intradermal tests showed positive reactions to the drug at the indicated dilution in all but one case. In Case 6, the BAT was performed using the contrast agent iopamidol, but the result was negative. Numerical values in the drug concentration columns indicate the concentration of the culprit drug that most activated basophils. The proportion of activated basophils when the basophils were most highly activated is shown in the activated basophils columns. The percentage of activated basophils was obtained by subtracting 5%, which is the value activated by the negative control. Patients who showed no response to positive controls are displayed as non-responders. BAT, basophil activation test; IDT, intradermal test; ND, no data; SPT, skin prick test.

Case	Skin tests			Basophil activation tests					
	SPT	IDT (mg ml ⁻¹)	Delay in skin tests (days)	CD203c		CD63		Results of BATs	Delay in BATs (days)
				Drug concentration (mg ml ⁻¹)	Activated basophils (%)	Drug concentration (mg ml ⁻¹)	Activated basophils (%)		
1	ND	0.1	54	—	—	—	—	ND	—
2	ND	1	43	—	—	—	—	ND	—
3	Negative	0.01	33	—	—	—	—	ND	—
4	Negative	0.02	61	3	25.4	—	—	Positive	61
5	Negative	0.2	55	3	49.4	—	—	Positive	55
6	Negative	Negative	58	0.6	2.2	—	—	Negative	58
7	Negative	0.2	82	0.6	-1.6	3	2.4	Negative	82
8	Negative	0.02	48	0.6	5.2	0.06	9	Positive	48
9	Negative	0.1	35	ND	ND	ND	ND	Non-responder	35
10	Negative	0.1	66	10	0.9	—	—	Negative	66
11	Negative	0.02	46	10	7.1	10	5.1	Positive	46
12	Negative	0.2	28	10	57.2	10	49.2	Positive	28

Discussion

Eighteen cases of anaphylaxis occurred during the study period, six of which were caused by sugammadex. The incidence of anaphylaxis, calculated by dividing the number of patients who developed anaphylaxis by the number who received each drug, was 0.02% for sugammadex (six/29 962) and 0% for neostigmine (zero/3157). Sugammadex had a market share of >90% amongst antagonists to NMBAs, and was administered in about 60% of general anaesthesia cases. Based on the number of vials used and drug sales, sugammadex rapidly gained a large market share immediately after its release in Japan. Our online survey suggested that the reason for the popularity of sugammadex was the certainty and rapidity of antagonism of neuromuscular block.

The incidence of sugammadex-induced anaphylaxis in our study (0.02%) was comparable with that estimated from post-marketing surveillance in the USA (0.024%)¹⁰ and lower than that in a previously reported Japanese single-institutional study (0.039%).¹¹ The former study is expected to be accurate

for the number of patients who received sugammadex, but not for the number who developed anaphylaxis to it because it contains the assumption that only 10% of occurrences are reported.¹⁰ The latter study is limited in that diagnosis was made without performing diagnostic tests, such as skin tests.¹¹ Although the suspected causative agents of anaphylaxis are often gauged by assessing the time of administration of each drug in relation to symptom onset, this approach is not recommended in the complex perioperative setting. Indeed, by using this approach, previous studies have shown that the correct allergen is missed in a substantial number of patients.^{27,28} In this study, all patients diagnosed with sugammadex-induced anaphylaxis were positive for skin tests. As we confirmed a positive reaction by BAT in all but one case with positive skin tests, we believe that our diagnosis is accurate. To the best of our knowledge, this is the first study to determine the incidence of anaphylaxis attributable to neostigmine.

In determining the number of drug-induced anaphylaxis cases, in addition to the incidence of anaphylaxis, the

Table 6 Usage of neuromuscular blocking agents and their reversal agents. The usage rate of drugs was calculated by dividing the number of patients receiving each drug by the total number of patients receiving general anaesthesia. The usage rate of drugs in cases with NMBAs was calculated by dividing the number of patients receiving each drug by the total number of patients receiving NMBAs. The share was calculated from the usage rate of each drug amongst the categorised drugs.

Neuromuscular blocking agents				Reversal agents			
Drug	Number of patients	Overall usage rate (%)	Share (%)	Drug	Number of patients	Overall usage rate (%)	Usage rate amongst cases with NMBAs (%)
Rocuronium	44 692	90.2	95.7	Sugammadex	29 962	60.5	64.2
Vecuronium	246	0.5	0.5	Neostigmine	3157	6.4	6.8
Succinylcholine	1749	3.5	3.7				
Total	46 687	94.3	100.0		33 119	66.9	70.9

frequency of drug use is an important factor to be considered. Indeed, sugammadex had a market share of about 90% as an antagonist of NMBAs in this study. Conversely, a recent UK study showed that neostigmine was used in 92% of all reversed cases.²⁹ One of the reasons for this disparity might be the differences in the NMBAs used in the UK and in Japan. The share of NMBAs in the UK shown by the National Audit Project 6 (NAP6) was atracurium (45%), rocuronium (38%), and succinylcholine (10%),²⁹ whilst only rocuronium, vecuronium, and succinylcholine are commercially available in Japan. In our study, the share of rocuronium was 95.7%, and those of vecuronium and succinylcholine were 0.5% and 3.7%, respectively. In addition to the share of each NMBA, the overall high rate of the use of all NMBAs in the current study is also noteworthy: 94.3% of patients who received general anaesthesia were administered NMBAs, whilst the NMBA usage rate reported in the NAP6 was 47%.²⁹ Of patients undergoing general anaesthesia who received NMBAs, antagonists were used in 70.9% of cases in our study, compared with 62% in NAP6. Therefore, in general anaesthesia cases, antagonists to NMBAs are used 2.3 times more often in Japan than in the UK. Given the share of sugammadex in each country (90.5% vs 9.1%), the amount of sugammadex used per the amount of sugammadex used per case of general anaesthesia in Japan is expected to be 22.8 times greater than that in the UK. The low incidence of sugammadex-induced anaphylaxis in NAP6 (0.0016%) can also be explained by the fact that the NAP6 included only severe Grades 3–5 cases.⁷ Alternatively, possible racial difference in the incidence of sugammadex-induced anaphylaxis might contribute to the difference.

Nearly 100% of respondents stated that they have free access to sugammadex at their hospital. Conversely, in the rest of the world, only 46% of respondents answered that sugammadex was available and relevant to their practice.³⁰ In most countries, the main barrier to the use of sugammadex is cost.^{30,31} Sugammadex is generally expensive; a dose of Atvagoreverse® (a mixture of neostigmine and atropine 6 ml) costs about US \$6, whilst a 200 mg dose of sugammadex costs about \$90.¹⁴ However, concern about adverse effects, and not cost, was the most common reason for not using sugammadex amongst survey respondents in this study. The popularity of sugammadex in Japan might result from the nationwide health insurance system, because this system substantially reduces patients' financial burden, and hence, many Japanese anaesthesia professionals are unlikely to consider price when they select drugs for use during anaesthesia.¹⁴

The current study suggests that neostigmine might be safer than sugammadex when assessing only the incidence of anaphylaxis. In addition to anaphylaxis, concerns about the side-effects of sugammadex, including serious adverse cardiac events, laryngospasm, and bronchospasm, have recently been reported.^{32–35} We believe that there is room to reconsider the choice of NMBA reversal agent for all anaesthetists, even in countries other than Japan. A good candidate for the use of sugammadex would be a patient with a high risk of residual neuromuscular block. Conversely, neostigmine should be given to patients who have a history of allergic reactions to sugammadex or who have no specific reason that suggests the need for sugammadex.

In several randomised studies of healthy non-anaesthetised volunteers, dose-dependent hypersensitivity or anaphylaxis reactions to sugammadex were observed even without prior administration of an NMBA.^{36,37} The incidence of anaphylaxis was reportedly very low, and neither elevated

blood concentrations of tryptase nor sugammadex-specific IgE or IgG antibodies were observed in any cases in those studies. The elevated concentrations of tryptase in the current study, however, suggested the involvement of activated mast cells as the underlying mechanism of sugammadex-induced anaphylaxis in some patients. Moreover, activated basophils might have contributed to the onset of anaphylaxis, because positive reactions in BAT were seen in most patients. As the mechanism(s) by which mast cells and basophils are activated remain unresolved, it would be too early to conclude anything about the mechanism of anaphylaxis attributable to sugammadex.

In this study, potential cases of anaphylaxis were identified by attending anaesthetists. Although we have implemented several measures to minimise the under-reporting of suspected anaphylaxis cases in participating hospitals, the possibility of under-reporting cannot be completely ruled out. Another possible limitation of this study is that fewer patients received neostigmine compared with sugammadex. Further, it would be ideal if the backgrounds of patients who received sugammadex and neostigmine were adjusted for variables that could lead to potential biases. As the current study utilised data from four hospitals located in a restricted area, selection bias might have occurred. A larger prospective study will be required in the future to better clarify the incidence of sugammadex-induced anaphylaxis.

In conclusion, our study provides more detailed information on the incidence of sugammadex-induced anaphylaxis than has been reported previously. Sugammadex has been widely used since its release and currently accounts for the majority of antagonists to neuromuscular blocking agents used in Japan. It remains a useful alternative to neostigmine from several points of view, although its routine use deserves careful consideration. Anaesthetists should be aware of the possibility of anaphylaxis with administration of sugammadex, and should observe patients for an appropriate period of time after its administration.

Authors' contributions

Study concept/design: all authors.

Data collection/analysis/interpretation: MO, TT.

Writing of paper and responsibility for its contents: all authors.

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Declarations of Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2019.10.016>.

References

References

- Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg* 2007; **104**: 575–81
- Abad-Gurumeta A, Ripolles-Melchor J, Casans-Frances R, et al. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. *Anaesthesia* 2015; **70**: 1441–52
- Carron M, Zarantonello F, Tellaroli P, Ori C. Efficacy and safety of sugammadex compared to neostigmine for reversal of neuromuscular blockade: a meta-analysis of randomized controlled trials. *J Clin Anesth* 2016; **35**: 1–12
- Hristovska AM, Duch P, Allingstrup M, Afshari A. The comparative efficacy and safety of sugammadex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic review with meta-analysis and trial sequential analysis. *Anaesthesia* 2018; **73**: 631–41
- Paton F, Paulden M, Chambers D, et al. Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. *Br J Anaesth* 2010; **105**: 558–67
- Mertes PM, Alla F, Trechot P, Auroy Y, Jouglu E. Groupe d'Etudes des Réactions Anaphylactoïdes Per-anesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011; **128**: 366–73
- Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
- Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. *Anaesthesia* 2014; **69**: 1251–7
- Takazawa T, Tomita Y, Yoshida N, et al. Three suspected cases of sugammadex-induced anaphylactic shock. *BMC Anesthesiol* 2014; **14**: 92
- Food and Drug Administration. NDA 22225: sugammadex injection. In: *Anesthetic and analgesic drug products advisory committee (AC) meeting*; November 6, 2015. sugammadex AC briefing document. Available from: <https://www.fda.gov/oc/resources/files/11-15/110615-merck.pdf?1520874794>. [Accessed 21 April 2019]
- Miyazaki Y, Sunaga H, Kida K, et al. Incidence of anaphylaxis associated with sugammadex. *Anesth Analg* 2018; **126**: 1505–8
- Seed MJ, Ewan PW. Anaphylaxis caused by neostigmine. *Anaesthesia* 2000; **55**: 574–5
- Hermite L, Louvier N, Hilaire P, Orry D, Seltzer S, Collet E. Neostigmine induced anaphylaxis in the wake of surgery. *Anaesth Crit Care Pain Med* 2015; **34**: 109–11
- Takazawa T, Miyasaka K, Sawa T, Iida H. Current status of sugammadex usage and the occurrence of sugammadex-induced anaphylaxis in Japan. *APSF NewsL* 2018; **33**: 11–2
- Takazawa T, Sabato V, Ebo DG. In vitro diagnostic tests for perioperative hypersensitivity, a narrative review: potential, limitations, and perspectives. *Br J Anaesth* 2019; **123**: e117–25
- Hopkins PM, Cooke PJ, Clarke RC, et al. Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions. *Br J Anaesth* 2019; **123**: 29–37
- Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; **57**: 45–51
- Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
- Ue KL, Kasternow B, Wagner A, Rutkowski R, Rutkowski K. Sugammadex: an emerging trigger of intraoperative anaphylaxis. *Ann Allergy Asthma Immunol* 2016; **117**: 714–6
- Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012; **157**: 215–25
- Baretto RL, Beck S, Heslegrave J, et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: a perioperative perspective. *Allergy* 2017; **72**: 2031–4
- Horiuchi T, Yokohama A, Orihara M, et al. Usefulness of basophil activation tests for diagnosis of sugammadex-induced anaphylaxis. *Anesth Analg* 2018; **126**: 1509–16
- Takazawa T, Horiuchi T, Yoshida N, Yokohama A, Saito S. Flow cytometric investigation of sugammadex-induced anaphylaxis. *Br J Anaesth* 2015; **114**: 858–9
- Garcia-Ortega P, Marin A. Usefulness of the basophil activation test (BAT) in the diagnosis of life-threatening drug anaphylaxis. *Allergy* 2010; **65**: 1204
- Torres MJ, Romano A, Blanca-Lopez N, et al. Immuno-globulin E-mediated hypersensitivity to amoxicillin: in vivo and in vitro comparative studies between an injectable therapeutic compound and a new commercial compound. *Clin Exp Allergy* 2011; **41**: 1595–601
- Christiansen IS, Kroigaard M, Mosbech H, Skov PS, Poulsen LK, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; **45**: 807–14
- Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br J Anaesth* 2005; **95**: 468–71
- Marinho S, Kemp H, Cook TM, et al. Cross-sectional study of perioperative drug and allergen exposure in UK practice in 2016: the 6th National Audit Project (NAP6) Allergen Survey. *Br J Anaesth* 2018; **121**: 146–58
- O'Reilly-Shah VN, Wolf FA, Jabaley CS, Lynde GC. Using a worldwide in-app survey to explore sugammadex usage patterns: a prospective observational study. *Br J Anaesth* 2017; **119**: 333–5
- Savic L, Savic S, Hopkins PM. Sugammadex: the sting in the tail? *Br J Anaesth* 2018; **121**: 694–7
- Hunter JM, Naguib M. Sugammadex-induced bradycardia and asystole: how great is the risk? *Br J Anaesth* 2018; **121**: 8–12
- Greenaway S, Shah S, Dancey M. Sugammadex and laryngospasm. *Anaesthesia* 2017; **72**: 412–3
- Wu TS, Tseng WC, Lai HC, Huang YH, Wu ZF. Sugammadex and laryngospasm. *J Clin Anesth* 2019; **56**: 52

35. Baronos S, Selvaraj BJ, Liang M, Ahmed K, Yarmush J. Sugammadex-induced bronchospasm during desflurane anaesthesia. *Br J Anaesth* 2019; **123**: e155–6
36. de Kam PJ, Nolte H, Good S, et al. Sugammadex hypersensitivity and underlying mechanisms: a randomised study of healthy non-anaesthetised volunteers. *Br J Anaesth* 2018; **121**: 758–67
37. Min KC, Bondiskey P, Schulz V, et al. Hypersensitivity incidence after sugammadex administration in healthy subjects: a randomised controlled trial. *Br J Anaesth* 2018; **121**: 749–57

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Supplemental Table 1

Questions and answers in the survey questionnaire for anaesthetists

Question 1	Choices
Are you in an environment where you can freely use sugammadex?	Yes or No
Question 2	
What is your rate of use of sugammadex as an antagonist to NMBAs?	Continuous variable from 0 to 100
Question 3	
Select your reason(s) for choosing sugammadex, in order of importance, from among the following options.	1. Certainty of antagonism of muscle relaxation, including for deep muscular blockade 2. Safety of antagonism of muscle relaxation with few adverse effects 3. Rapidity of antagonism of muscle relaxation 4. No particular reason 5. Others
Question 4	
Select your reason(s) for <u>not choosing</u> sugammadex, in order of importance, from the following options.	1. Existence of an alternative drug, neostigmine 2. Concerns about adverse events, including the occurrence of anaphylaxis 3. Cost or cost benefit concerns 4. No particular reason 5. Others