



Comparison of sugammadex and neostigmine in terms of the incidence of anaphylaxis: A retrospective multicenter observational study

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6 **Comparison of sugammadex and neostigmine in terms of the incidence of**
7 **anaphylaxis: A retrospective multicentre observational study**
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10 **Running title**

11 Anaphylaxis due to sugammadex and neostigmine
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Abstract

Background

Although cases of anaphylaxis caused by sugammadex have been reported, its exact incidence remains unknown. Conversely, no studies have evaluated the incidence of anaphylaxis due to neostigmine.

Methods

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

Results

A total of 49,532 cases who received general anaesthesia were included in this study. During the study period, 18 cases of anaphylaxis occurred, of which six were due to sugammadex and none to neostigmine. There were no fatalities due to anaphylaxis. The incidence of anaphylaxis caused by all drugs and that by sugammadex was calculated as 0.036% (95%CI: 0.022%-0.057%) and 0.02% (of the number of sugammadex cases) (95%CI: 0.007%-0.044%), respectively.

Conclusion

In this study, the incidence of anaphylaxis due to sugammadex was estimated to be 0.02% and there were no cases of anaphylaxis due to neostigmine during the study period. These 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

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6 choice of reversal agent for NMBAs by all **anaesthetists**, even in countries other than
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8 Japan.
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13 **Keywords:**

14 anaphylaxis, sugammadex, neostigmine, skin tests, basophil activation tests,
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16 neuromuscular blocking agents
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22 **Clinical trial registration:**

23 UMIN000022365, UMIN000033561
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Introduction

Sugammadex is a synthetic cyclodextrin derivative that encapsulates aminosteroid muscle relaxants, especially rocuronium, to reverse their effect ¹. Sugammadex was developed to overcome the problems with neostigmine, including occasional incomplete reversal of muscle relaxation and the need for 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 demonstrated the advantages of sugammadex versus neostigmine in terms of recovery time from both moderate and deep neuromuscular blockade 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. Since the incidence of perioperative hypersensitivity is quite low, at one case in thousand to tens of thousands^{6,7}, more extensive studies are needed to correctly estimate the incidence of hypersensitivity to individual drugs, including sugammadex and neostigmine.

A significant number of cases with sugammadex-induced anaphylaxis have been previously reported ^{8,9}. According to the post-marketing safety database, approximately 11.5 million patients in the USA had received sugammadex as of 31 March 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 Japanese single centre study, six cases of anaphylaxis were suspected to be caused by sugammadex during a three-year study period. This study estimated the incidence of sugammadex-induced

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6 anaphylaxis to be approximately 1 in 2500 cases (0.039%) based on a study population
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8 of 15,479 patients ¹¹. In a 1-year study of perioperative anaphylaxis in the UK, only one
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10 confirmed case of sugammadex anaphylaxis was reported from among an estimated
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12 64,000 administrations (0.0016%) ⁷. On the other hand, the incidence of neostigmine-
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14 induced anaphylaxis is unknown, although there are few case reports of anaphylaxis due
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16 to neostigmine ^{12, 13}.

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19 While sugammadex appears to be used only in a limited number of cases in many
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21 countries due to its high cost, it is used routinely in Japan, and an estimated 10% of the
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23 population received sugammadex during an 8-year period from 2010 to 2018 ¹⁴. However,
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25 it is not clear how the use of sugammadex progressed in Japan during this period, and
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27 why the use of sugammadex is more frequent than in other countries.

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30 In this study, we retrospectively investigated the incidence of perioperative
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32 anaphylaxis in multiple **centres** in Japan over a 5-year period. In order to ensure the
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34 quality of diagnosis, only cases with a clinical history suggestive of anaphylaxis, along
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36 with positive results in *in vitro* or *in vivo* testing, were assessed ¹⁵. We compared the
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38 incidence of anaphylaxis caused by sugammadex and neostigmine directly, with the null
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40 hypothesis being that the incidence of anaphylaxis caused by sugammadex is higher than
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42 that by neostigmine. We also investigated the changes in usage of sugammadex and
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44 neostigmine over time by obtaining sales data of these drugs over an 8-year period, and
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46 conducted an online survey of **anaesthetists** across Japan to determine the reason for the
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48 popularity of sugammadex.
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54 **Methods**

55 **Subjects**

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6 This retrospective observational study conforms to the standards of the Declaration of
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8 Helsinki and was approved by the ethics committee of Gunma University Hospital. The
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10 study was registered with the University Hospital Medical Information Network Clinical
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12 Trials Registry (ID: 000022365, 000033561). This article adheres to Strengthening the
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14 Reporting of Observational Studies in Epidemiology (STROBE) guidelines. All
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16 consecutive cases of general anaesthesia in four Japanese hospitals, i.e. Gunma University
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18 Hospital, Isesaki Municipal Hospital, JCHO Gunma Chuo Hospital and Gunma Saiseikai
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20 Maebashi Hospital, between January 2012 and December 2016 were included. Since we
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22 aimed to collect data on anaphylaxis to all drugs administered, this study also included
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24 cases where no neuromuscular blocking agents (NMBAs) were used. We diagnosed
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26 anaphylaxis only when two or more of the following criteria were fulfilled: 1. Evaluation
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28 using the clinical monitoring scoring system suggested the possibility of an immediate
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30 hypersensitivity reaction (net total score on the clinical grading scale ≥ 8)¹⁶; 2. Skin tests
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32 and/or basophil activation tests showed a positive reaction to any of the drugs that the
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34 patient was exposed to during anaesthesia; and 3. Blood samples taken soon after the
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36 event showed an elevation in histamine and/or tryptase concentration. All participating
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38 hospitals used an electronic anaesthesia recording system, ensuring the accuracy of all
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40 intra-anaesthesia clinical information, including all medications and substances
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42 administered before the episode of anaphylaxis, the clinical features, and details of
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44 treatment. We obtained the relevant patient information, including allergy history and
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46 past surgical history.
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57 We collected data on the use of NMBAs and their antagonists at all participating
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6 hospitals between January 2009 and December 2016. Basically, the data were extracted
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8 from the electronic anaesthesia information management system at each hospital. At
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10 hospitals where such a system was not introduced, the operators extracted data from
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12 paper-based anaesthesia charts. Moreover, we purchased longitudinal medicine
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14 procurement data from IQVIA, Japan, to assess trends in the market share of NMBA
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16 antagonists throughout Japan between January 2009 and December 2016.
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20 21 Skin and blood tests

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23 Skin tests were performed in accordance with several international guidelines¹⁷⁻¹⁹. The
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25 recommended maximum drug concentration for skin prick tests (SPTs) for most drugs is
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27 an undiluted concentration, while that for intradermal tests (IDTs) is a 10-fold dilution¹⁷,
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29¹⁹. Bifurcated needles (Tokyo M.I. Co. Inc., Tokyo, Japan) were used for SPTs. SPT
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31 reactions were considered positive when the size of the wheal increased by 3 mm or more
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33 in diameter after 20 min and was associated with a flare¹⁹. IDTs were performed with
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35 26-gauge needles (Terumo Co., Tokyo, Japan) to create a post-injection wheal of up to 4
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37 mm in diameter. IDT reactions were deemed positive when the diameter of the
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39 reactionary erythematous wheal was equal to at least twice that of the post-injection wheal
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41 after 20 min¹⁹. In most cases, we performed SPTs first, and performed IDTs only when
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43 the SPTs showed negative reactions.¹⁸⁻²⁰
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50 Optional blood tests to measure plasma histamine and serum tryptase concentrations
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52 were performed in most cases. The threshold concentration of histamine that was
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54 considered to indicate an elevated level was set at 1 ng mL⁻¹. We determined that serum
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56 tryptase concentration was elevated when peak tryptase levels exceeded 1.2 x baseline
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58 tryptase + 2 µg L⁻¹^{21,22}. Blood samples were collected at the earliest opportunity after the
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6 start of the reactions in the operation room. A baseline sample was also obtained 24 h
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8 after the reaction.
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10 11 12 Basophil activation tests

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15 The methods of the BAT are detailed elsewhere ^{23, 24}. Briefly, whole blood samples
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17 were obtained from patients with allergic reactions. All the BATs were performed using
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19 a flow cytometer (BD FACSCanto™ II Flowcytometer, Japan BD Co., Tokyo, Japan).
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21 For detecting activated basophils, an Allergenicity kit (Beckman Coulter Inc., Tokyo,
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23 Japan) was used within 4 h after blood sampling. Blood samples were incubated with
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25 serial dilutions of culprit agents at 37°C. Anti-IgE-antibody and phosphate buffered saline
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27 (PBS) were used as positive and negative controls, respectively. The samples were stained
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29 with 20 µL of a mixture containing anti-CRTH2-FITC, anti-CD203c-PE, and anti-CD3-
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31 PC7-conjugated antibodies. Basophils were selected based on a side scatter and low CD3-
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33 /CRTH2+ gate profile and at least 500 basophils were counted. Furthermore, the number
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35 of basophils with CD63 was counted in another set of samples. A maximum of 5%
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37 spontaneous expression of CD203c and CD63 after stimulation with the buffer solution
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39 (negative control) was tolerated. The BAT was considered positive when the basophil
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41 stimulation index (drug / control) was ≥ 2 , provided more than 5% drug-activated
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43 basophils were detected ^{25, 26}.
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51 Online survey

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53 An online survey was conducted to explore the use of reversal agents and the attitude
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55 of **anaesthetists** towards these agents. A total of 93 **anaesthetists** were invited to
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57 participate in this survey. The survey was constructed and distributed using “Survey
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6 Monkey”, a commercially available online survey vehicle. The subjects were divided into
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8 two groups: Group A comprised 46 **anaesthetists** who had worked at the participating
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10 hospitals for at least one year between January 2012 and December 2016. Group B
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12 comprised 47 **anaesthetists** who participated in the Japanese epidemiologic study for
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14 perioperative anaphylaxis, which is an ongoing prospective **multicentre** observational
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16 study on perioperative anaphylaxis. Both groups were included as we sought to survey
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18 not only **anaesthetists** at the participating hospitals, but also Japanese **anaesthetists** in
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20 general. The survey comprised four questions, as shown in Supplemental Table 1. The
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22 survey was available online for one month (August 2018 for Group A and September
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24 2018 for Group B). Responses to questions 3 and 4 were scored using a scale: the first
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26 item had a score of five points, the second four points, the third three points, the fourth
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28 two points, and the fifth one point.
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35 Statistical analysis

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37 The incidence of anaphylaxis was calculated as the fraction of the number of confirmed
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39 cases of anaphylaxis versus the number of general anaesthesia cases. The 95% confidence
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41 interval (CI) for incidence was calculated by the Clopper-Pearson method using Sigma
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43 Plot 14.0 software (Systat Software Inc., San Jose, CA, USA).
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48 Results

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50 A total of 49,532 cases who received general anaesthesia were included in this study.
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52 The number of patients who were given reversal agents and those who developed
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54 anaphylaxis are shown in Table 1. During the study period, 23 suspected cases of
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56 anaphylaxis occurred, of which 18 cases were confirmed as anaphylaxis (Grade II: 6 cases,
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6 Grade III: 10 cases, Grade IV: 2 cases), six of which were in response to sugammadex
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8 (Grade II: 2 cases, Grade III: 4 cases) and none to neostigmine (Supplemental Figure 1).
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10 The total number of patients who received sugammadex during the study period was
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12 29,962 and the incidence of sugammadex-induced anaphylaxis was six. As a result, the
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14 incidence of anaphylaxis caused by all drugs and that by sugammadex was calculated as
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16 0.036% (95%CI: 0.022%-0.057%) and 0.02% (95%CI: 0.007%-0.044%), respectively
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19 (Table 1).
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22 The details of sugammadex-induced anaphylaxis cases are summarized in Table 2. All
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24 patients met the diagnostic criteria of anaphylaxis, because they showed sufficient
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26 symptoms to suspect anaphylaxis after exposure to sugammadex and had positive
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28 reactions in skin tests to sugammadex. Although the timing of blood sampling in the
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30 operation room varied from 10 to 90 min after the episode, both histamine and tryptase
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32 levels were increased in all three patients tested. Baseline levels of these substances in
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34 these patients were below the threshold. Although four patients required treatment with
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36 epinephrine, all patients recovered with no major problems, including a biphasic reaction.
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38 All patients showed positive reactions to sugammadex either in SPTs or IDTs that were
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40 performed 4-9 weeks after the episode. Moreover, BATs showed positive reactions to
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42 sugammadex in all patients tested (n = 5). These results suggested that sugammadex was
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44 indeed the most likely causative agent of anaphylaxis in all six cases.
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49 Information on the patients who developed anaphylaxis to agents other than
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51 sugammadex is shown in Table 3. As in the patients with sugammadex-induced
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53 anaphylaxis, all 12 patients fulfilled the diagnostic criteria of anaphylaxis.
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56 In order to examine the background factors related to anaphylaxis caused by
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58 sugammadex, we investigated the usage of NMBAs in the participating hospitals. The
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6 total number of patients who received NMBA during the study period was 46,687, of
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8 whom 44,692 (95.7%) received rocuronium (Table 4). The total number of patients who
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10 received antagonists to NMBA during the study period was 33,119, of whom 29,962
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12 (90.5%) received sugammadex (Table 4).
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15 The chronological changes in the usage ratios of antagonists to NMBA at participating
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17 hospitals are shown in Supplemental Figure 2A. Even though sugammadex was launched
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19 in Japan in April 2010, its average usage rate had already reached nearly 80% in 2011.
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21 The transition of NMBA antagonist usage at participating hospitals and the transition of
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23 total sales throughout Japan are shown in Supplemental Figure 2B for sugammadex and
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25 Supplemental Figure 2C for neostigmine. The number of cases using sugammadex
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27 increased dramatically and those using neostigmine decreased during the study period.
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29 This trend was consistent with the sales data of both drugs.
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33 The response rate of the online survey was 97.8%, as 91 out of 93 **anaesthetists**
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35 answered the questionnaire. The median duration of experience in clinical anesthesiology
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37 practice among the respondents was 18 years. There were no significant differences in
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39 the background characteristics of **anaesthetists** and their responses in the survey in the
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41 two groups. Therefore, the results of the questionnaire were described by adding the
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43 results of the two groups. For question 1, 97.8% (89 out of 91) of responders answered
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45 that they use sugammadex as they wish. For question 2, the average rate of sugammadex
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47 usage was $90.6 \pm 17.7\%$. The results for questions 3 and 4 are summarized in
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49 Supplemental Figures 3A and 3B, respectively. The top three reasons for choosing
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51 sugammadex were certainty, rapidity, and safety of muscle relaxation antagonism, while
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53 the main reasons for not choosing sugammadex were concerns about adverse effects,
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55 followed by cost or cost benefit concerns.
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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 (6 / 29,962) and 0% for neostigmine (0 / 3,157). Sugammadex had a market share of more than 90% among antagonists to NMBAs and was administered in about 60% of general anaesthesia cases. The data based on the number of vials used and drug sales demonstrated that 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 muscle relaxation.

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 in response to it, because it contains the assumption that only 10% of occurrences are reported¹⁰. The latter study is limited in that diagnosis was made without performing additional diagnostic tests, such as skin tests¹¹. 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

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6 sugammadex-induced anaphylaxis were positive for skin tests. Since we confirmed a
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8 positive reaction by BATs in all but one case with positive skin tests, we believe that our
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10 diagnosis is accurate. Moreover, to the best of our knowledge, this is the first study to
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12 demonstrate the incidence of anaphylaxis due to neostigmine.
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15 In determining the number of drug-induced anaphylaxis cases, in addition to the
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17 incidence of anaphylaxis, the frequency of drug use is an important factor to be considered.
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19 Indeed, sugammadex had a market share of about 90% as an antagonist of NMBAs in this
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21 study. Conversely, a recent UK study showed that neostigmine was used in 92% of all
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23 reversed cases ²⁹. One of the reasons for this disparity might be due to differences in the
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25 muscle relaxants used in the UK and Japan. The share of muscle relaxants in the UK,
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27 shown by the National Audit Project 6 (NAP6), was in the order of atracurium (45%),
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29 rocuronium (38%), and succinylcholine (10%) ²⁹, while only rocuronium, vecuronium
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31 and succinylcholine are commercially available in Japan. Indeed, in our study, the share
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33 of rocuronium was overwhelming at 95.7%, and that of vecuronium and succinylcholine
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35 were 0.5% and 3.7%, respectively. In addition to the share of each NMBA, the overall
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37 high usage rate of all NMBAs in the current study is also noteworthy: 94.3% of patients
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39 who received general anaesthesia were administered NMBAs, while the NMBA usage
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41 rate reported in the NAP6 was 47% ²⁹. Furthermore, of the patients with general
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43 anaesthesia who received NMBAs, antagonists were used in 70.9% of cases in our study,
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45 compared to 62% in NAP6. Thus, in general anaesthesia cases, antagonists to NMBAs
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47 are used 2.3 times more often in Japan than in the UK. Given the share of sugammadex
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49 in each country (90.5% vs. 9.1%), the amount of sugammadex used per unit of general
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51 anaesthesia in Japan is expected to be 22.8 times greater than that in the UK. The low
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53 incidence of sugammadex-induced anaphylaxis in the NAP6 (0.0016%) can also be
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6 explained by the fact that the NAP6 included only severe grade 3-5 cases ⁷. Alternatively,
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8 the possible racial difference in the incidence of sugammadex-induced anaphylaxis might
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10 also be a potential reason for the difference.
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13 Nearly 100% of respondents stated that they have free access to sugammadex at their
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15 hospital. Conversely, in the rest of the world, only 46% of respondents answered that
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17 sugammadex was available and relevant to their practice ³⁰. In most countries, the main
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19 barrier to the use of sugammadex is cost ^{30, 31}. Sugammadex is generally expensive; a
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21 dose of atvagoreverse® (a mixture of neostigmine and atropine, 6 mL) costs about \$6 US,
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23 while a 200 mg dose of sugammadex costs about \$90 ¹⁴. Surprisingly, however, concerns
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25 about adverse effects, and not the cost, was the most common reason for not using
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27 sugammadex among survey respondents in this study (Supplemental Figure 3). The
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29 popularity of sugammadex in Japan might result from the nationwide health insurance
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31 system, because this system substantially reduces the patient's financial burden, and
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33 hence, many Japanese anaesthesia professionals are unlikely to consider price when they
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35 select drugs for use during anaesthesia ¹⁴.
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40 The current study suggested that neostigmine might be safer than sugammadex when
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42 assessing only the incidence of anaphylaxis. Moreover, besides anaphylaxis, concerns
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44 about the side effects of sugammadex, including serious adverse cardiac events and
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46 laryngospasm, have recently been reported ³²⁻³⁴. We believe that there is room to
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48 reconsider the choice of NMBA reversal agent for all **anaesthetists**, even in countries
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50 other than Japan. A good candidate for use of sugammadex would be a patient with a high
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52 risk of residual muscle relaxation. Conversely, neostigmine should be given to patients
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54 who have a history of allergic reactions to sugammadex or who have no actual reason that
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56 specifically suggests the need for sugammadex.
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6 In several randomized studies of healthy non-anaesthetized volunteers, dose-dependent
7 hypersensitivity or anaphylaxis reactions to sugammadex were observed even without
8 prior administration of an NMBA ^{35,36}. The incidence of anaphylaxis was reportedly very
9 low, and neither elevated blood levels of tryptase nor sugammadex-specific IgE or IgG
10 antibodies were observed in any of the cases in those studies. The elevated levels of
11 tryptase in the current study, however, suggested involvement of activated mast cells as
12 the underlying mechanism of sugammadex-induced anaphylaxis in some patients.
13 Moreover, activated basophils might have contributed to the onset of anaphylaxis,
14 because positive reactions in BATs were seen in most patients. Since the mechanism(s)
15 by which mast cells and basophils are activated remain unresolved, it would be too early
16 to conclude anything about the mechanism of anaphylaxis due to sugammadex.
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30 In this study, potential cases of anaphylaxis were identified by attending **anaesthetists**.
31 Although we have implemented several measures to minimize underreporting of
32 suspected anaphylaxis cases in all the participating hospitals, the possibility of
33 underreporting cannot be completely ruled out. Another possible limitation of this study
34 is that fewer patients received neostigmine compared to patients who received
35 sugammadex. Further, it would be ideal if the backgrounds of patients who received
36 sugammadex and neostigmine were adjusted for variables that could lead to potential
37 biases. Since the current study utilized data from four hospitals located in a restricted
38 area, selection bias might have occurred. A larger prospective study will be required in
39 future to better clarify the incidence of sugammadex-induced anaphylaxis.
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53 In conclusion, our study provides more precise information on the incidence of
54 sugammadex-induced anaphylaxis than has been reported previously. Sugammadex has
55 been widely used since its release and currently accounts for the majority of antagonists
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6 to NMBAAs used in Japan. It remains a useful alternative to neostigmine from several
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8 points of view, although its routine use deserves careful consideration. **Anaesthetists**
9
10 should be aware of the possibility of anaphylaxis with the administration of sugammadex
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12 and should observe patients for an appropriate period of time after its administration.
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17 **Author contributions**

18
19 Study concept/design: all authors

20
21 Data collection, analysis, and interpretation: MO and TT

22
23 Writing of the paper and responsibility for its contents: all authors
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For Peer Review

Table 1
Summary of the number of perioperative anaphylaxis events due to antagonists to NMBAs and other drugs

Hospital	Number of cases with GA	Number of cases each drug was used		All cases of anaphylaxis			Caused by SUG			Caused by NEO		
		SUG	NEO	Anaphylaxis	Incidence (%)	95%CI (%)	Anaphylaxis	Incidence (%)	95%CI (%)	Anaphylaxis	Incidence (%)	95%CI (%)
A	23358	12149	1447	6	0.026	0.009-0.056	1	0.008	0.000-0.046	0	0.000	0.000
B	11773	6912	1374	5	0.042	0.014-0.099	3	0.043	0.009-0.127	0	0.000	0.000
C	8112	5983	116	3	0.037	0.008-0.108	1	0.017	0.000-0.093	0	0.000	0.000
D	6289	4918	220	4	0.064	0.017-0.163	1	0.020	0.001-0.113	0	0.000	0.000
All	49532	29962	3157	18	0.036	0.022-0.057	6	0.020	0.007-0.044	0	0.000	0.000

Abbreviations: GA, general anaesthesia; SUG, sugammadex; NEO, neostigmine; CI, confidence interval

Table 2

A: Clinical background, anaphylactic symptoms and blood test results in patients with anaphylaxis due to sugammadex

Case	Age (years)	Sex	Height (cm)	Weight (kg)	ASA PS	Previous surgical history	Previous exposure to SUG	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 mmHg HR: 120 bpm Thoracic erythema	25	15	-	-	-	-
2	34	M	159	62	1	No	No	1	BP: 70/40 mmHg Generalized erythema	19	4	-	-	-	-
3	13	M	159	40	1	No	No	5	BP: unmeasurable HR: 160 bpm Facial swelling Elevated AP	30	20	-	-	-	-
4	65	M	168	65	2	Yes	Yes	<1	BP: 40/25 mmHg Generalized 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 mmHg HR: 130 bpm Thoracic erythema	17	11	49.3	1.1	22.0	2.8
6	62	M	159	57	1	UI	UI	3	BP 45/20 mmHg Nausea	13	19	7.0	0.3	104.0	5.8

All patients had a clinical score of 8 or above, suggesting possible anaphylaxis¹⁶. Anaphylactic symptoms appeared after 80 mg of sugammadex administration in case 3 and 200 mg of sugammadex in other cases. A past history of drug allergies was present in only case 4, as allergy to contrast media.

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status classification; SUG, sugammadex; F, female; BP, blood pressure; HR, heart rate; M, male; AP, airway pressure

B: Results of skin tests and basophil activation tests in patients with anaphylaxis following sugammadex administration

Case	Skin tests			CD203c		CD63		Result of BATs	Delay in BATs (months)
	SPT (mg mL ⁻¹)	IDT (mg mL ⁻¹)	Delay in skin tests (days)	SUG concentration (mg mL ⁻¹)	Activated basophils (%)	SUG 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

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 of sugammadex represents the undiluted / full-strength solution. The concentration of sugammadex and 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 study²³.

Abbreviations: BAT, basophil activation tests; SPT, skin prick tests; IDT, intradermal tests; SUG, sugammadex; ND, no data

Table 3

A: Clinical background, anaphylactic symptoms and blood test results in patients with anaphylaxis induced by drugs other than sugammadex

Case	Age (years)	Sex	Height (cm)	Weight (kg)	ASA PS	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	Base line
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 mmHg 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 mmHg HR: 170 bpm Elevated AP Decrease in SpO ₂ to 82%	35	30	34.9	0.9	35.3	3.9

1																
2	4	71	F	149	53	2	No	Cefazolin	10	BP: 40/18 mmHg	21	5	11.0	0.8	13.2	2.9
3										Generalized wheal						
4										and erythema						
5																
6																
7	5	26	F	168	56	2	No	Cefazolin	2	BP: 34/21 mmHg	26	26	115.0	1.0	17.7	2.5
8										HR: 133 bpm						
9										Unmeasured SpO ₂						
10																
11	6	83	F	157	59	2	Yes	Unidentified	Unknown	BP: 40/25 mmHg	16	80	11.3	0.7	19.5	3.9
12										HR: 125 bpm						
13										Elevated AP to 25						
14										cmH ₂ O						
15																
16																
17	7	56	M	179	83	2	Yes	Cefoperazone	5	VF	32	35	1.7	1.3	31.9	3.6
18																
19								-Sulbactam		Elevated AP						
20																
21	8	67	F	160	48	2	No	Cefazolin	3	BP: 60/45 mmHg	21	30	9.6	0.9	2.4	1.2
22										HR: 120 bpm						
23										Generalized						
24										erythema						
25																
26																
27	9	78	F	155	50	2	Unknown	Rocuronium	10	BP: 65/37 mmHg	19	5	0.8	0.7	2.9	1.8
28										Elevated AP						
29										Generalized						
30										erythema						
31																
32																
33	10	21	M	180	67	1	Yes	Flurbiprofen	10	BP: 64/32 mmHg	20	30	54.0	0.8	7.3	2.8
34										HR: 120 bpm						
35										Generalized						
36										erythema and						
37										itching						

11	7	F	132	28	2	No	Cefazolin	10	BP: 40/22 mmHg HR: 140 bpm 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 mmHg HR: 140 bpm Erythema at right upper limb	12	15	49.1	0.1	5.0	3.6

All patients had a clinical score of 8 or more, suggesting possible anaphylaxis¹⁶. A past history of drug allergies to ciprofloxacin was seen in case 6 and to tropicamide in case 8.

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status classification; F, female; M, male; AP, airway pressure; BP, blood pressure; HR, heart rate; VF, ventricular fibrillation

B: Results of skin tests and basophil activation tests in subjects with anaphylaxis to drugs other than NMBA antagonists

Case	Skin tests			BATs			Results of BATs	Delay in BATs (days)	
	SPT	IDT (mg mL ⁻¹)	Delay in skin tests (days)	CD203c Drug concentration (mg mL ⁻¹)	Activated basophils (%)	CD63 Drug concentration (mg mL ⁻¹)			Activated basophils (%)
1	ND	0.1	54	-	-	-	-	ND	-
2	ND	1	43	-	-	-	-	ND	-
3	negative	0.01	33	-	-	-	-	ND	-

1											
2	4	negative	0.02	61	3	25.4	-	-	positive	61	
3											
4	5	negative	0.2	55	3	49.4	-	-	positive	55	
5	6	negative	negative	58	0.6	2.2	-	-	negative	58	
6											
7	7	negative	0.2	82	0.6	-1.6	3	2.4	negative	82	
8	8	negative	0.02	48	0.6	5.2	0.06	9	positive	48	
9											
10	9	negative	0.1	35	ND	ND	ND	ND	non-responder	35	
11	10	negative	0.1	66	10	0.9	-	-	negative	66	
12											
13	11	negative	0.02	46	10	7.1	10	5.1	positive	46	
14	12	negative	0.2	28	10	57.2	10	49.2	positive	28	
15											
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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.

Abbreviations: BAT, basophil activation tests; SPT, skin prick tests; IDT, intradermal tests; ND, no data

1
2 Table 4
3
4 Usage of neuromuscular blocking agents and their reversal agents
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NMBAs				Reversal agents				
Drug	Number of patients	Overall usage rate (%)	Share (%)	Drug	Number of patients	Overall usage rate (%)	Usage rate among cases with NMBAs (%)	Share (%)
Rocuronium	44692	90.2	95.7	Sugammadex	29962	60.5	64.2	90.5
Vecuronium	246	0.5	0.5	Neostigmine	3157	6.4	6.8	9.5
Succinylcholine	1749	3.5	3.7	Total	33119	66.9	70.9	100.0
Total	46687	94.3	100.0					

22 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.
23 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
24 NMBAs. The share was calculated from the usage rate of each drug among the categorized drugs.
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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.	<ol style="list-style-type: none"> 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.	<ol style="list-style-type: none"> 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

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3 Supplemental Figure 1

4 Flow diagram of the study

5 The criteria fulfilled in each case are underlined.
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9 Supplemental Figure 2

10 A: Chronological changes in the usage ratios of each NMBA antagonist. The average and standard
11 deviation of all the hospitals' shares are shown. B and C: Chronological changes in the total number
12 of cases using antagonists to NMBAs at three of the hospitals and the number of their sales in Japan
13 as a whole. Since sugammadex was first released in Japan in 2010, the number of cases using
14 sugammadex (red open circles) and number of vials of sugammadex sold (red closed circles) were
15 calculated considering those of 2011 as 100% (B). The number of cases using neostigmine (blue open
16 circles) and number of vials of neostigmine sold (blue closed circles) were calculated considering those
17 of 2009 as 100% (C).
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24 Supplemental Figure 3

25 Results of the online survey of **anaesthetists**. Reason(s) for choosing sugammadex (A) and reason(s)
26 for not choosing sugammadex (B) are shown. Each item was scored for ranking: The first item had a
27 score of five points, the second four points, the third three points, the fourth two points, and the fifth
28 one point. The total score of each item is displayed next to each bar. The number of reasons cited by
29 one respondent ranged from one to five, because the number of reasons was not specified. Therefore,
30 the total number of points for figure A and B does not match (922 vs. 637).
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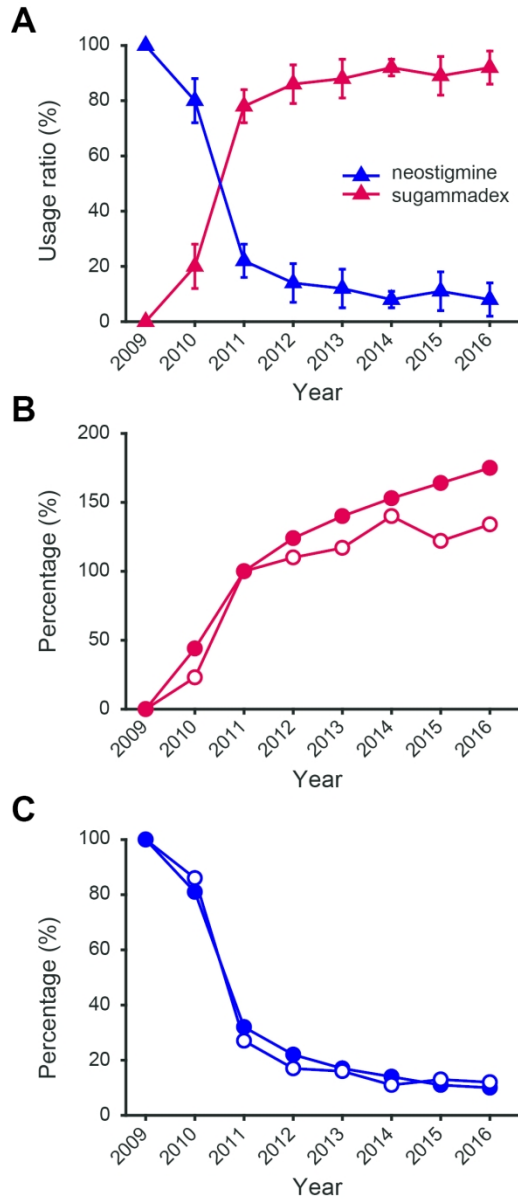
Suspected cases of anaphylaxis (n = 23)

Excluded (n = 5)

- The clinical score was 11, blood tests and skin test were not performed
- The clinical score was 7, blood tests showed positive results, skin tests were not performed
- The clinical score was 7, blood tests showed negative results, skin tests showed positive results
- The clinical score was 14, blood tests showed negative results, skin tests were not performed
- The clinical score was 26, baseline data of blood tests were missing, skin tests showed negative results

Included in the study (n = 18)

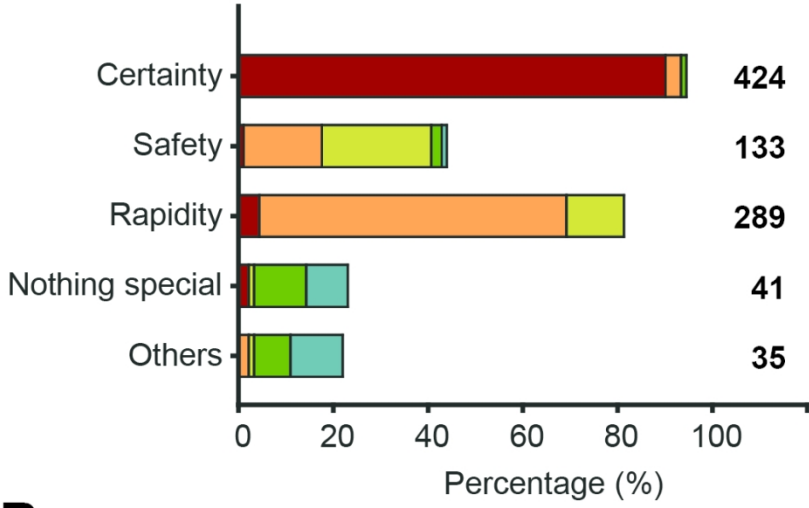
- Sugammadex-induced anaphylaxis (n = 6)
- Anaphylaxis induced by drugs other than sugammadex (n = 12)



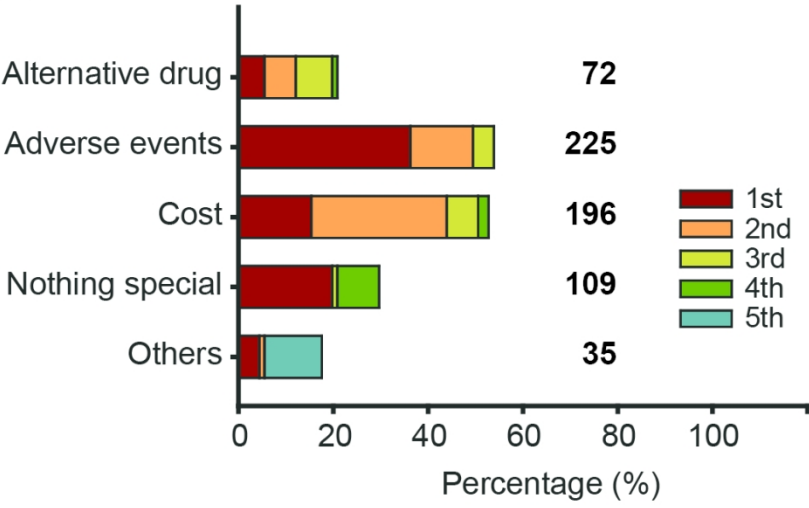
Supplemental Figure 2

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A



B



Supplemental Figure 3