Author's response to reviews

Title: Three suspected cases of sugammadex-induced anaphylactic shock

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Author's response to reviews: see over
Dear Dr. Rowles,

Thank you very much for your e-mail dated February 24, 2014, concerning our manuscript entitled “Three suspected cases of sugammadex-induced anaphylactic shock”, together with the reviewers’ comments. We are very glad to know that our manuscript will be considered for publication in *BMC Anesthesiology* pending appropriate revision.

We have carefully examined the reviewers’ comments and replied to all their concerns.

Finally, we are grateful to the reviewers for their careful reading of our manuscript and their thoughtful criticisms. We believe our manuscript has been strengthened as a result of our efforts to address these comments.

We have responded to each of the comments raised by the reviewers as follows.

Reviewer 1

1. In addition to the Godai et al. and Menendez-Ozcoidi et al. references quoted, there have been at least 3 other brief reports on possible allergic reactions to sugammadex -- 2 in Japan (Matsui 2012: 61: 746 &749) and 1 in Europe (Clin Drug Invest 2010: 30: 867). For completeness, and to provide a report that is as up-to-date as possible for others, the authors might think about including coverage of these reports.

Reply: In the Japanese literature mentioned above (Masui 2012: 61: 749), the authors concluded that the direct cause of difficult bag mask ventilation after sugammadex administration seemed to be laryngeal spasm due to light anesthesia rather than a
sugammadex-induced allergic reaction. Hence, we did not include this reference. We have, however, included the other two recommended references in the reference list and discussed it in the text.

2. Bronchospasm may be a possibility when sugammadex is given to patients with underlying pulmonary symptoms. The authors should consider this and comment if they think it might be relevant in any way to their findings.

Reply: We agree that pulmonary symptoms in case 1 may have been due to bronchospasm (Please see page 9 line 1 in the original version), because a past report has shown that bronchospasm was observed in 39.8% of cases of anaphylaxis[1].

Reviewer 2

1. I suggest rewriting the first sentence of the abstract. Mind that sugammadex is not really that recent anymore. The authors might adapt as follows: “Sugammadex has a unique mechanism of action and is widely used because of its safety and efficacy”

Reply: We made the required change in accordance with the comment.

2. There is no point in trying to overestimate this case report; this is not the first report on so-called life-threatening anaphylaxis to sugammadex. Previous reports were about serious clinical presentations too, and, moreover, there is not such a thing as life-threatening anaphylaxis or no-life-threatening anaphylaxis; every case of allergy/anaphylaxis is worrisome! The authors should thus keep things simple and ‘reduce’ the importance of their findings in their abstract and manuscript, as follows, e.g. ‘We hereby describe another series of cases of possible anaphylaxis against sugammadex’. This is already interesting enough!

Reply: We modified the description in the revised manuscript in accordance with the above comment.

3. Case presentation: better is “All three patients received general anesthesia with rocuronium and their tracheas were intubated.”
   “…for reversal of rocuronium effect”; delete ‘effect’.
   ‘Along with mucocutaneous erythema’; delete ‘signs, including’
Adapt: ‘difficulty in manual ventilation’

Reply: We modified the text in accordance with all the comments.

4. Conclusion: delete: ‘The Japanese society... This is consistent ...in 2012’; it has no place here. The only conclusion is as follows: “Our findings suggest that physicians using sugammadex should be aware of the possibility of sugammadex-induced anaphylaxis”. Drugs for treating anaphylaxis need to be available always in the operating room environment, so leave this out of the conclusion.

Reply: We modified the text in accordance with the comment.

5. I suggest shortening the first paragraph of the ‘background’ section and retaining only what follows: “Sugammadex is widely used in more than 60 countries, including the EU and Japan, for reversal of the effects of steroidal nmbas, such as rocuronium. The action ... acetylcholinesterase inhibitors, such as neostigmine.”

Reply: We modified the description of the study background in accordance with the comment.


Reply: We changed the literature citation as recommended.

7. ‘In one report...’: the authors should be careful with statements that allergic reactions are ‘mild’: re-intubation is not a low-grade complication!

Reply: The sentences regarding the severity of allergic reactions in previous reports were deleted.

8. Delete the entire paragraph starting with “In 2012, we encountered ...four
thousand cases”. It has no sense to ‘estimate’ allergy incidences based on assumptions about commercial use and the data gathered in your hospital. Instead, you could make a general statement on the use of sugammadex in Japan, being that it is ‘regularly and widely used’.

Reply: The sentence was deleted, as recommended.

9. The methodology is rare: from six cases, the authors describe three: what about the other three? They had negative skin tests for sugammadex? Or no testing at all? Moreover, I do not think it is an issue here: just simply describe the three cases and omit mentioning the entire background on how the authors came to the six (?)/three suspected cases. The authors are invited to re-write as follows: e.g. ‘We describe 3 cases in which positive skin test reactions against sugammadex were observed’.

Reply: Skin tests were performed in 3 out of 6 patients in whom sugammadex-induced anaphylactic shock was suspected. As recommended, we have decided to describe only the 3 patients in whom skin tests were performed.

10. Case 1: no opioids during induction of anesthesia? Only remifentanil for maintenance, not for induction? This needs to be clarified.

Reply: We routinely use remifentanil for induction. The dose of remifentanil in all the cases is now shown in the text.

11. Oxygen saturation was normal: do not use descriptions like ‘in the range of...”. The same for blood pressure.

Reply: We think that mentioning the numerical value of vital signs before the events helps to understand the rate of its decrease. Therefore, we decided to retain the values, including those of oxygen saturation and blood pressure.

12. Adapt as follows: ‘Before extubation, sugammadex 2 mg/kg iv was administered...’

Reply: We modified the description in accordance with the comment.

13. The same for ‘Extubated when breathing spontaneously and fully awake’. And for
‘Blood pressure fell to unmeasurable values’. This all considerably shortens the manuscript.

Reply: We made the required modifications in accordance with these comments.

14. The authors did no test for latex? Antibiotics? Chlorhexidine? Other disinfectants? This needs considerable attention.

Reply: All the equipment and materials used in our operation rooms are latex free. Antibiotics were not used in these cases, although we use antibiotics in most cases. It is difficult to exclude the possibility that disinfectants may have been a cause of anaphylaxis. However, given the timing of disinfection (i.e. before the surgery), we think this was not the case in our patients.

15. Omit the sentence commencing with ‘Despite this treatment…’. Adrenaline was given, the patient was in anaphylaxis, enough arguments to explain the tachycardia. I would delete the suggestion of the hypercarbia. As well as the statement on the ‘bag-mask ventilation’. Just mention that the patient needed to be re-intubated.

Reply: We have incorporated these suggestions in this revision.

16. Why the choice for rocuronium for re-use after sugammadex: although I agree that there is evidence for re-use with high-dose rocuronium, shouldn’t it be more prudent to use e.g. a benzylisoquinoline? Please comment.

Reply: Unfortunately, no benzylisoquinoline muscle relaxants are commercially available in Japan. We did not have vecuronium available either. Therefore, we chose a relatively high-dose of rocuronium even after sugammadex administration.

17. Ropivacaine was tested; when had it been given?

Reply: The surgeon injected ropivacaine at the site of the wound just before the surgery.

18. The authors did not check for tryptase levels although it can easily be done even some time after anaphylaxis occurs (up to probably 4hrs after an event, it may have sense). It could have been very reliable here. Unfortunately the authors did
not do. It should be addressed why.

Reply: We agree that tryptase levels should have been checked. Please see the last sentence in the third paragraph of the discussion.

19. As in the other case presentations, I would keep description of maintenance anesthesia quite simple: reduce the information e.g. as follows: “anesthesia was maintained with sevoflurane and remifentanil”.

Reply: We abbreviated the description in accordance with the comment.

20. At the end of page 6: delete the sentence “No allergic signs, including mucocutaneous reactions, were seen at this time.”

Reply: The sentence was deleted, as recommended.

21. It is clear from the second and third cases that in your practice, sugammadex dosing is based very often on a vial-basis, one vial containing 200mg. This is an unfortunate practice, as sugammadex, like other drugs, should be dosed on a mg/kg basis and according to the dose requirements described by the manufacturer (for which neuromuscular monitoring is a necessity). When sugammadex is administered on a routine basis without appropriate dose adaptations based on NMT monitoring, the drug may not be reliable at all (see: Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. Kotake Y, Ochiai R, Suzuki T, Ogawa S, Takagi S, Ozaki M, Nakatsuka I, Takeda J. Anesth Analg. 2013 Aug;117(2):345-51).

Reply: We agree that sugammadex should be dosed on a mg/kg basis and its appropriate dose should be based on NMT monitoring. We added these comments in the text. Please see the fifth paragraph of the discussion.

22. Erythema of the precordium? Do you mean ‘thoracic erythema’, or something else?

Reply: We have changed the description to thoracic erythema.

23. Next sentence: change into: “No respiratory symptoms...were observed”.

Reply: We have changed the description to thoracic erythema.
Further: ‘the patient was transferred to the icu’, instead of ‘moved to’.

Reply: We made modifications in accordance with these comments.

24. Case 3 The first sentence on page 8: simplify by ‘during induction and maintenance of anesthesia, blood pressure, oxygen saturation and end-tidal CO2 were within normal ranges’.

Reply: We modified the manuscript in accordance with the comment.

25. It is unclear from the authors’ description if the patient’s trachea was extubated when symptoms occurred.

Reply: The patient’s trachea was still intubated when symptoms occurred. We have clarified this in the text.

26. Discussion: delete the entire paragraph on the Ring criteria.

Reply: The Ring criteria were deleted.

27. Discussion, page 9: indeed, as already earlier mentioned in this review, tryptase should have been determined: the authors should comment on this.

Reply: We agree that tryptase levels should have been checked. Please see the last sentence in the third paragraph of the discussion regarding this.

28. Discussion, page 10: as the authors state themselves, there remains a problem with these case descriptions, being that there were no histamine controls; the authors should comment on this.

Reply: We agree that histamine as a positive control should be used for skin tests. Please see the fourth paragraph of the discussion.

29. Second paragraph on page 10: simplify by reformulating as follows: “cyclodextrins are present in various foods and this may partly explain cross-reaction with sugammadex”
30. I am not sure where the authors get the allergic reactions from to 'higher' clinical doses (sugammadex>16mg/kg is moreover not a clinically used dose anymore, see manufacturer's dose requirements). In the paper by Godai et al (BJA 2012) three times a 'lower' dose of sugammadex was administered, causing anaphylaxis.

Reply: Indeed, the manufacturer recommends using 2 mg/kg or 4 mg/kg sugammadex to reverse the effect of rocuronium, depending on its residual effect. However, 16 mg/kg sugammadex is recommended by the manufacturer when the effect of rocuronium needs to be reversed immediately after its administration (within 3 minutes), as in anesthesia for electroconvulsive therapy [2]. Thus, in comparison, we think around 3 mg/kg is a low clinical dose.

31. Last paragraph of the discussion: I suppose the authors want to suggest that there is OR a high incidence of sugammadex-related allergy in Japan (more than in other populations? Reasons? Possible explanations?) OR that there is a ‘normal’ incidence of sugammadex-related allergy in Japan, but that sugammadex is used in Japan more than in other countries. I therefore suggest introducing the above and deleting the sentence in the manuscript starting with ‘These warnings…’.

Reply: We have made a major modification in the discussion in accordance with the comment. Please see the text.

32. The authors suggest correctly that sugammadex anaphylaxis is typically presenting when the patient is already extubated, put into bed, being transferred to the PACU or ICU etc.: typically timepoints when a patient is less monitored and when less access is available to drugs and resuscitation material (during transfer to the PACU for example). This is an important issue and should be stressed in the discussion. I suggest, however, deleting "Indeed, anaphylaxis, while not a common reaction, is a serious allergic reaction that is rapid in onset and capable of causing death. Moreover, it is difficult to predict the timing and severity of anaphylaxis. In particular, sugammadex-induced anaphylactic shock occurs at a dangerous time, i.e., just after extubation.”

Reply: We have deleted the sentences as recommended by the reviewer.
Reviewer 3

1. As 95 clinical cases of identical adverse reactions are recorded for this alert by the Japanese Society of Anaesthesia it would be of interest to cite it in bibliography or as foot note in this article.

Reply: The citation of the alert is not shown in the bibliography, because the alert was written in Japanese. Instead, we have added more information about this alert in the discussion.

2. Authors must provide the sampling times and the values of markers (plasmatic concentrations of histamine and tryptase) that are mentioned in the discussion.

Reply: While we are aware that plasma concentrations of histamine and tryptase should be checked in suspected anaphylaxis cases, we were unable to perform blood tests for histamine and tryptase in our cases.

3. On the other hand, injected IDR in healthy volunteers with no skin reaction are not known with sugammadex while for many drugs used in the perioperative period they have been studied and published (Mertes et al, Anesthesiology 2007. 107:245). This is important for the interpretation of skin tests reported by the authors and must be longer discussed.

Reply: Clarke et al have reported that dilutions of 100 mg/ml sugammadex at 1:77 and 1:770 did not cause skin irritation or false positive reactions in 11 volunteers [3]. In addition, a recent report has suggested that a suitable intradermal skin test dilution appears to be 1:100 [4]. A previous report has shown that positive skin-prick test results were obtained with a sugammadex dilution of 1:10 in one patient and 1:1000 in another [5]. However, further studies are needed to clarify suitable sugammadex dilutions for allergy testing. Please see the discussion section of the manuscript for this.

Reviewer 4

1. Sugammadex has not been approved yet by the FDA and also a second attempt has recently failed. Therefore delete the sentence.
2. It might have been interesting if the authors would have included all 6 cases. Why
were they excluded: only because of the absence of negative skin testing? Negative skin
tests may still suggest an allergic event such as a complement mediated reaction.

Reply: We believe that all 6 cases were likely to be sugammadex induced anaphylaxis.
However, skin tests were not performed in 3 of the 6 cases. In our opinion, since it is
difficult to argue about a causative agent without performing skin tests, we have
included only 3 cases in this report.

3. A positive skin test may be suggestive for an IgE mediated reaction or direct histamin
release. IgE mediated reactions are usually severe while the authors themselves admint
that up to now most reported reactions were rather mild. Seems contradictory

Reply: We have quoted more case reports for sugammadex-induced anaphylaxis. The
word “mild” was deleted.

4. Skin prick tests are usually performed with the undiluted substance (why diluted in
case 1?) as opposed to IDT. What are the recommended dilutions for sugammadex? An
IDT test is positive only when the flare increases with more concentrated injectates e.g.
from 1/1000 to 1/10 or from 1/10000 to 1/100. Why was a skin prick testing performed in
case 1 (positive so no additional IDT indicated) while in case 2 and 3 only the IDT was
done without skin prick testing?

Reply: In several guidelines [6-8], 1:10 diluted or undiluted drugs are recommended for
use in a skin prick test. However, there are no guidelines for allergy testing,
particularly for sugammadex, so far. A previous report used diluted sugammadex for
the skin prick test in order to avoid false-positive results [5]. Performing both skin prick
and intradermal tests may be ideal for reaching a correct diagnosis. In our cases, we
performed either the skin prick test or intradermal test to minimize the risk of
recurrence of anaphylaxis. However, we are aware that there is a risk of false-positive
results when only an intradermal test is performed.

5. Why was skin testing not performed with histamine as a control? Why was latex not
tested as reactions to latex may be delayed and therefore underestimated? Latex may be tested by IgE testing (RIA/RAST).

Reply: We agree that histamine should be used for skin testing as a positive control. However, histamine was not approved in our hospital at that time, because it is not a therapeutic drug. Latex was less likely to be an antigen in our cases, because our operation rooms are latex free. However, we agree that latex should be included when testing for allergy to drugs.

6. Sampling for tryptase levels can be done after resuscitation, another one to three hours after the reaction (peak level) and one supplemental after 24 hrs as a control. So the argument that there was no time due to the resuscitation attempts does not stand here.

Reply: We agree that tryptase levels can be checked even after resuscitation. Please see the last sentence in the third paragraph of the revised discussion.

7. An incidence of 1 in 4000 administrations seems quite unbelievable to me. In this calculations all 6 cases (why?) were considered while such incidence would be similar to that for rocuronium itself.

Reply: The sentences describing estimated incidence of possible anaphylaxis against sugammadex were deleted.

8. All cases lack significant information about duration of surgery
   - what was given at what time point?
   - was neuromuscular function monitored?
   - how was decided which dose of sugammadex should be given (2mg/Kg, 2.8mg/kg or 3.2mg/kg)?
   - what were the conditions the patient had to present to decide extubation?
   - why were propofol doses so low?
   - when prolonged ventilation at ICU was necessary, what kind of sedation did patients receive?

Reply: The duration of surgery is now shown in the text. We did not monitor neuromuscular function in any of the cases. Instead, anesthesiologists judged the dose
of sugammadex from the dose and timing of the last administration of sugammadex and respiratory conditions in patients, in a comprehensive way. However, we agree that neuromuscular monitoring should be used for decision-making. The dose of propofol used in the three cases was 2 mg/kg, 1.83 mg/kg, and 1.61 mg/kg, respectively. Mention of the additional dose of propofol in case 2 was missed in the original version. Given the late onset of anaphylaxis against sugammadex, the patient’s trachea was extubated in the ICU 17 hours after the event in case 1. Midazolam was used as the sedative drug for prolonged postoperative ventilation.

9. Case 1. I can imagine that after injection of sugammadex and waiting for awakening, adequate respiration .... at least 5 minutes will elapse. It is difficult to believe that at the moment of extubation no single sign was observed suggestive for an adverse event of any kind. When at the moment of the reaction a 'low consciousness level' was noticed, how was consciousness then at the time of extubation? Hydrocortisone is not first line treatment.

Reply: The patient did not have a problem with ventilation at extubation (normal airway pressure, normal SpO$_2$). Blood pressure was also normal, although it had been measured up to 2.5 minutes prior to extubation. We are not sure whether low blood pressure was missed because of intermittent measurement. However, the patient was not completely conscious at extubation. Another explanation for the normal parameters at the time of extubation is relatively slow onset (> 5 minutes) of anaphylactic reactions (please see reply for Q16). We agree that hydrocortisone is a secondary, and not a primary, treatment strategy for anaphylaxis.

10. Case 2. Why was first phenylephrine given?

Reply: The first line of treatment of anaphylaxis is adrenaline. However, the resident anesthesiologist in case 2 did not suspect anaphylactic shock at first and hence, administered phenylephrine rather than adrenaline.

11. Case 3. Was surely the mildest case with moderate hypotension and reversal with ephedrine (so no adrenaline).

Reply: At first, the anesthesiologist did not suspect anaphylactic shock because of mild hypotension in case 3. Hence, ephedrine was administered, which resulted in reversal of
12. How do the authors explain that none of the three cases suffered bronchospasm?
The authors mention some respiratory impact in case 1 but never report wheezing or
high inspiratory peak pressures... although they gave aminophilline which is not
immediately the best treatment option as it will accentuate tachycardia (which was
already present). So only the \( \text{paCO}_2 \) of 66.4 mmHg (how was it measured in the
extubated patient ?) suggested respiratory impairment or might simply be explained by
carbon dioxide exhalation following the pneumoperitoneum.

Reply: We think that bronchospasm did occur in case 1 (Please see page 9 line 1 in the
original version), because the patient had a low \( \text{SpO}_2 \) level and bag mask ventilation
was difficult. \( \text{PaCO}_2 \) was measured by the single blood sampling from femoral artery
followed by blood gas analysis, because we did not have time to insert an arterial
cannula in the emergency situation.

13. For the diagnosis of an anaphylactic syndrome there should ideally be three positive
tests including skin tests, basophil activation test (BAT because mast cells are not the
only ones involved in IgE mediated reactions) and IgE tests.
In all present cases only the clinical history i.e. a reaction suggestive for an allergic
event some minutes after the injection of the last given substance and a positive
(correctly performed ?) skin test (which may be false positive) are the only indicators.

Reply: We agree that skin tests, basophil activation tests, and IgE tests are helpful in
the diagnosis of anaphylaxis. A sentence describing the need for these tests was added
in the discussion.

14. The june 2013 warning by JSA at least merits to be referenced.

Reply: We have added more information about this warning in the discussion.

15. Equipment and medication to treat a possible adverse event should ALWAYS be
available when injecting any perioperative substance.

Reply: Reviewer 2 has also pointed out the same thing. Hence, the conclusion was
shortened in accordance with this comment.
16. Discussion, last sentence: In particular...occurs at a dangerous time i.e. just after extubation. Are we extubating too rapidly then? Or are reactions to sugammadex slower than other anaphylactic reactions?

Reply: In the 2013 warning by the JSA, it has been reported that the percentages of anaphylactic reactions against sugammadex that appeared within 5 and 10 minutes were 65.8% (50/76) and 86.8% (66/76), respectively. This data suggests that anaphylactic reactions to sugammadex may appear just after extubation when extubation is performed within 5 minutes after administration of sugammadex.

Reviewer 5

1. They claim this is the first cases of anaphylaxis to be attributed to Sugammadex, but there are several other publications describing anaphylaxis, including reference 2 (Godai) in which case 2 would fulfill the Sampson criteria for anaphylaxis. The authors should make an up to date literature search and change the text accordingly.

Reply: We modified the text in accordance with the comment.

2. Even though there have been several reports of anaphylaxis/hypersensitivity reactions to Sugammadex from different countries these authors have a new angle as they comment on a possible incidence of hypersensitivity to Sugammadex in a particular area of Japan. They should include some more data on the frequency of use of Sugammadex in Japan and the suggested rate of hypersensitivity reactions: Also some more detail on the warning issued by the Japanese Society of Anesthesiologists in June 2013 might be of interest to the anaesthetic community in countries using Sugammadex.

Reply: We have added more information about sugammadex usage in Japan. Moreover, more details on the JSA warning have also been added.

3. Although timing of the reactions all coincided with Sugammadex administration there were other drugs co-administered and it should be made clear that all drugs and substances should be tested. The authors have only tested drugs, but latex and chlorhexidine are also known to cause perioperative anaphylaxis and should be
included for testing. In fact in Japan in the 1980’s warnings were given against the use of high concentrations of chlorhexidine on mucous membrane due to cases of perioperative anaphylaxis. The authors should mention this and suggest that testing includes latex and chlorhexidine.

Reply: We don’t exclude the possibility of late-onset allergic reactions induced by chlorhexidine in cases 1 and 2. However, in case 3, povidone iodine was used as the disinfectant. Further, in our patients, latex was less likely to be an antigen, because our operation rooms are latex free.

4. Serum tryptase was not taken at the time of reaction for any of the three cases. The authors should make it even more clear that a blood sample for tryptase should be taken if possible. The profile is such that elevations are still seen at least 1-2 hours after onset of the reaction at which stage the patient should be stabilized so a blood sample can be taken.

Reply: Sentences describing the importance and sampling time of serum tryptase measurements have been added in the discussion section of the revised manuscript.

5. The authors conclude that anaesthesiologist should be aware of the potential of Sugammadex to cause hypersensitivity reactions. In fact all drugs administered during anaesthesia have the potential to cause hypersensitivity reactions and anaesthesiologist should always be prepared to diagnose and treat anaphylaxis regardless of the cause. The authors are encouraged to include a few sentences on the recommended treatment of perioperative anaphylaxis as a learning point.

Reply: The treatment of anaphylaxis is mentioned in the last sentence of the discussion.

6. Page 2 line 4 Please delete statement that this is the first report describing anaphylaxis probably due to Sugammadex and revise according to results of a new updated literature search.

Reply: The corresponding sentence was deleted and a few more updated literature references were added.

7. Page 4 line 2 – are there really surgeons administering sugammadex? Also a very
long sentence could you rephrase or split it up?
Page 4 line 3 – please delete “such as” and make it clear that Sugammadex only works with rocuronium and vecuronium.

Reply: We modified the description in accordance with the comment.

9. Page 4 lines 4-8 The description of the mechanism of action of Sugammadex should be made shorter and clearer.

Reply: The description of the mechanism of action of sugammadex has been made shorter, as recommended.

10. Page 4 line 12 please check you ref 2 (Godai) case 2 had BP< 50 systolic, drop in saturation from 99% to 83% and took 42 minutes to improve on epinephrine and norepinephrine. I would not characterize that as “relatively mild”. Please adjust the text accordingly.

Reply: We modified the text in accordance with the comment.

11. Page 5 line 2 can you be sure that Sugammadex was the cause in the three cases with negative skin testing? Were they tested and if so did they test positive for other drugs? This is important if you are trying to calculate the incidence.

Reply: We have decided to only describe the 3 cases in which skin tests were performed.

12. Page 6 line 4 In theory rocuronium should not work just after the administration of Sugammadex – pleas comment on this.

Reply: In case 1, rocuronium was the sole non-depolarizing muscle relaxant available in our operation room, because vecuronium was not available. In addition, benzylisoquinoline muscle relaxants are not commercially available in Japan. Therefore, we decided to use rocuronium after administration of sugammadex. The amount of sugammadex molecules not bound with rocuronium was difficult to estimate. We used a relatively high-dose of rocuronium (1.3 mg/kg) to overcome this problem. As a result, the intubation was successfully performed without any adverse effects, such as stimulation of the cough reflex.
13. Page 7 line 6 – how was adrenaline administered intramuscularly or intravenously. Please add the route of administration. If a bolus dose of 0.5 mg was given iv, you need to comment that this is a larger dose than recommended in guidelines for the treatment of perioperative anaphylaxis. See ref 7 or Kroggaard M, Garvey LH, Gilberg L, Johansson SGO, Mosbech H, Florvaag E et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. Acta Anaesthesiol Scand 2007; 51: 655-70 (review) or Reducing the risk of anaphylaxis during anaesthesia: 2011 updated guidelines for clinical practice. Mertes PM, Malinovsky JM, Jouffroy L; working group of the SFAR and SFA, Aberer W, Tereehorst I, Brockow K, Demoly P; ENDA: EAACI Interest Group on Drug Allergy. J Investig Allergol Clin Immunol. 2011; 21: 442-53

Reply: Please see the description regarding bolus dose of adrenaline in the last paragraph of the discussion.

14. Page 9 line 1-4 It is good to use the Ring and Messmer classification but as they were all severe reactions defined as anaphylaxis by the Sampson criteria they are probably all class 3 according to Ring and Messmer.

Reply: Indeed, it was difficult to judge the severity of cases 2 and 3 using the Ring and Messmer classification, because these are obscure criteria. We have followed reviewer #2’s recommendation to delete the description of the Ring and Messmer classification.

15. Page 9 line 12 -15 please elaborate on the half-life of tryptase making it possible to sample tryptase 1-2 hours after a reaction.

Reply: Sentences were added to describe the importance and sampling time of serum tryptase measurements. Please see the discussion section of the revised manuscript for this.

16. Page 10 line 6 I agree that the sensitivity and specificity of skin tests with Sugammadex are not known. Did you test some healthy volunteers to get an idea about the irritant effect?

Reply: No, we did not. Instead, a past study testing the irritant effect of sugammadex in
volunteers was quoted.

17. Page 11 lines 2-7 please include some more detail about the JSA warning in June 2013. This is not really well known outside Japan and might be interesting to anaesthesiologists outside Japan.

Reply: Reviewer 3 and 4 also gave us similar feedback. We have added more information about this warning in the revised discussion.

18. Page 11 conclusion. Please consider that all drugs and substance can cause perioperative anaphylaxis and anaesthesiologist should always be ready to diagnose and treat anaphylaxis. Subsequently ideally investigations should be carried out with both allergological and anesthesiological expertise to make sure nothing is missed and appropriate tests are carried out.

Reply: We agree that, ideally, investigations using both allergological and anesthesiological expertise should be performed for correct diagnosis of perioperative anaphylaxis. However, we have followed the recommendation of one of the reviewers to simplify the conclusion and hence, have not elaborated on this in the text.

19. Table 1. Please include vial concentrations (eg propofol 10mg/ml) to avoid confusion about the exact concentrations used. What technique was used for intradermal test? How large was the initial bleb induced during injection?

Reply: Vial concentrations of the drugs used for skin tests are shown in a table. For intradermal tests, 0.05 ml diluted solutions of the drugs were injected into the dermis to create a bleb up to 4 mm in diameter.

20. Why was skin prick test not carried out in all cases?

Reply: Performing both skin prick and intradermal tests may be ideal for reaching a correct diagnosis. In our cases, we performed either the skin prick test or intradermal test to minimize the risk of recurrence of anaphylaxis. However, we are aware that there is a risk of false-positive results when only an intradermal test is performed.

1. Mertes PM, Laxenaire MC, Alla F, Groupe d'Etudes des Reactions Anaphylactoides


