Reviewer's report

Title: Three suspected cases of sugammadex-induced anaphylactic shock

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Reviewer: Guy Cammu

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Abstract, background: 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.”

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!

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’.

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.

Background
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.”

Next sentence: ‘…partly due to the lack of some undesirable effects’. Do not overestimate the side effects of neostigmine. Ref [1] should be a more general reference; there are better choices than the one the authors mention, e.g. Paton F, Paulden M, Chambers D, et al. Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a

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

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’.

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 (3)/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’.

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

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

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

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

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

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.

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.

Ropivacaine was tested; when had it been given?

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.

Case 2

Once more: no opioids for induction?

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”.

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

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).

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

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

Further: ‘the patient was transferred to the icu’, instead of ‘moved to’.

Once more: no testing for latex, antibiotics, disinfectants?

Case 3

No opioids for induction?

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’.

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

Discussion: delete the entire paragraph on the Ring criteria.

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

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.

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”.

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.

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…'.

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."

Suggest shortening the conclusion as follows (the rest is obvious): “We would advise physicians using sugammadex to be aware of the possibility of sugammadex-induced anaphylaxis.”

Ref 1, see previous comment.

Delete ref 5.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

In the past, G.C. has had funding for clinical trials of sugammadex from Organon/Schering-Plough/MSD. He has no current funding related to sugammadex.