Author’s response to reviews

Title: Preparing for the unexpected: Special considerations and complications after sugammadex administration

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Author’s response to reviews:

Dear Dr. Stefan Schaller

We thank reviewers for careful reading our manuscript and for fruitful suggestions. We have revised the manuscript on the basis of the reviewers’ comments. The new title of our manuscript will be “Preparing for the unexpected: Special considerations and complications after sugammadex administration”.

The original comments of the reviewers and our responses to them are as follows:

Comments of Dr. Stefan Schaller:

Major Points:

1. What is the purpose of the review? It is neither a systematic review, nor is it clearly defined in the introduction what questions the review shall answer. There are several review articles available for sugammadex even many cited by you. Please explain what your article adds to the current literature. Possibilities might be focusing on only very current research and pointing what has changed because of this new knowledge to earlier reviews (just as a suggestion).

We focused on the scenarios in which special attention is necessary after sugammadex administration.

To our knowledge, there is no review focused on this topic, so we hope our review will be clinically relevant and helpful. As the reviewer recommended, we rewrote the “Background” section.
2. After point 1 is clarified, please choose an appropriate title which displays the intention of this review.

We suggest that the new title of our manuscript be, “Preparing for the unexpected: Special considerations and complications after sugammadex administration”.

3. A review should not only mention the recommendations based on the drug information or Summary of Product Characteristics (SmPC). Therefore (a) present available literature where it is available (e.g. dosing of the drug in different depths of blockade, use in obesity) and (b) clearly state if a recommendation is based on the SmPC.

We have added several discussions, particularly in the “Sugammadex Use in Obese Patient” section, and have referenced them.

Minor Points

4. I am missing a reference at Page 8, line 12

We have added references, thank you for pointing this out.

5. I do not think that it is necessary to explain the history why we use TOF > 0.9 again. That has been well established nowadays; even more, there is a discussion to use 1.0 for acceleromyography.

We have added the reference and the following statement:

“It is also reported that electromyographic TOFR ≥0.9 and acceleromyographic TOFR of 1.0 signifies sufficient neuromuscular recovery (Baumuller et al., Piccioni et al.)”

6. Instead of citing several reports (e.g. for hypersensitivity) I suggest citing a paper where they have been summarized already.

We included some review articles as well as case reports. For example, we have cited a systematic review (Tsur et al) in the hypersensitivity section.

7. There are guidelines for treatment of anaphylaxis. I suggest citing one of the current ones.

Thank you for the suggestion. We have added the guidelines for treatment of anaphylaxis (World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015;8:32.).
8. What is the difference in testing hypersensitivity in sugammadex to any other substance should be described instead of a general description.

We have added the following statement:

“Testing for and treatment of sugammadex-induced anaphylaxis are not different from those of other allergens.”

9. Insert citations in Table 1 showing which evidence is supporting which statement and take account of point 3 above.

We have added citations in Table 1.

10. Cost considerations are only presented for the US. How is it in Japan, where widely used? What is with Europe?

We have added references and the following statements:

In Japan and Italy, sugammadex can be as much as 20 to 40 times the cost of traditional reversal agent, such as neostigmine (Ministry of Health Japan Injection price list, De Robertis et al.). Despite the cost difference between sugammadex and acetylcholinesterase inhibitors, Japan has a largest market share in the world because it has the reimbursement system in which additional costs can be charged directly to the patient (Schaller et al.).

Comments of Dr. Christoph Unterbuchner (Reviewer 1):

Dear Authors,

you have submitted a well written review about the possible new challenges after sugammadex administration.

The problems and safety challenges after sugammadex administration are described very detailed in the context of different pathologic stages.

There are some minor amendments that should be added in my opinion:

1) Thematic amendments:

a) It would be nice to get more information about the outcome (PORC, pulmonary), when sugammadex is compared to neostigmine.
The effect of routine availability of sugammadex on postoperative respiratory complications: a historical cohort study.

Olesnicky BL, Traill C, Marroquin-Harris FB.

Minerva Anestesiol. 2017 Mar;83(3):248 - 254

Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: sugammadex, neostigmine or no reversal.

Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, De Mel A, Tiong WS, Phillips M.


Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia.

Gaszynski T, Szewczyk T, Gaszynski W.


A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade.


Anaesthesia. 2015 Dec;70(12):1441-52

Postoperative impairment of motor function at train-of-four ratio ≥0.9 cannot be improved by sugammadex (1 mg kg⁻¹).

Baumüller E, Schaller SJ, Chiquito Lama Y, Frick CG, Bauhofer T, Eikermann M, Fink H, Blobner M.

Br J Anaesth. 2015 May;114(5):785-93

We focused on the PORC after sugammadex administration in this review. Therefore, we considered the comparison between sugammadex and neostigmine less informative. We have revised the section, and added the recommended articles (Gaszynski et al., Abad-Gurumeta et al., Baumüller et al.) in our manuscript.

b)Furthermore it would be very interesting for the reader to broach the use of sugammadex in orphan or neuromuscular disesaes:
Literature:

Anesthetic consideration for neuromuscular diseases.

Katz JA, Murphy GS.


Anaesthesia for thymectomy in adult and juvenile myasthenic patients.

Sungur Z, Sentürk M.

Curr Opin Anaesthesiol. 2016 Feb;29(1):14-9

Thank you for the helpful suggestion. However, after reading the references, we felt they addressed mostly the issues of “how to use” sugammadex, rather than the original focus of our review, “what happens” after sugammadex administration.

c) To my understanding use of sugammadex in children is slightly underrepresented:

Literature:

A comparison of sugammadex and neostigmine for reversal of rocuronium-induced neuromuscular blockade in children.

Ammar AS, Mahmoud KM, Kasemy ZA.


Current evidence for the use of sugammadex in children.

Tobias JD.

Paediatr Anaesth. 2017 Feb;27(2):118-125

We appreciate the reviewer’s suggestion, but we felt the review of pediatric use of sugammadex was not in the initial purview of our manuscript. We therefore opted not to include the use of sugammadex in children in our review.

2) General amendments:

a) Page 6, line 7: 2 mg/ kg BW is the dosing for the presence of at least two twitches, so this dosage is for moderate (TOF count 1-3) and shallow neuromuscular blockade (TOF count of 4 with fading).
We have deleted the “Characteristics and Clinical use of Sugammadex” section based on the other reviewer’s comments.

b) Page 7, line 1: It might be a clearer formulation to use reversing instead of antagonism, because encapsulation is another mechanism in comparison to antagonism with acetylcholine esterase inhibitors like neostigmine.

We have modified “antagonism” to “reversal”.

c) Page 9, line 9: In my opinion Brückmann’s study showed several methodological limitations, which should be mentioned. There were two letters which discussed this issue:

Is one acceleromyographically measured train-of-four ratio sufficient after sugammadex to identify residual curarization in postoperative, awake patients?

Unterbuchner C.


Sugammadex and residual neuromuscular block: what is acceptable normal practice?

Todd MM.


We have added the recommended references and the following statement:

“However, Unterbuchner (Unterbuchner et al.) and Todd (Todd et al.) have reported that high incidence of residual paralysis after antagonism with neostigmine was likely due to inappropriate intraoperative neuromuscular monitoring in this study.

d) Page 10, line 5: To my knowledge it is not possible to examine binding of all rocuronium molecules to sugammadex by quantitative neuromuscular monitoring.

An alternative formulation could be: On the one hand, there should be applied a dose of sugammadex adapted to the depth of neuromuscular blockade.

We have modified the sentence based on your advice.

e) Page 23, table 1, line 20: when dosed based on..., sounds not correct--> alternative formulation: dosing

We have modified “dosed” to “dosing”.

f) Page 23, table 1, line 32: Data were collected in mild hypothermia
g) Page 16, line 17: Carron instead of Caron

We have modified “Caron” to “Carron”.

3) Literature amendments:

Please insert citation in:

a) Page 8, line 3
b) Page 8, line 9
c) Page 8, line 14
d) Page 10, line 2
e) Page 10, line 12
f) Page 10, line 15
g) Page 11, line 10
f) Page 12, line 8
g) Page 13, line 9
h) Page 19, line 9
i) Page 19, line 11
j) Page 20, line 11
k) Page 23, table 1
l) Page 45, figure 2

We have added citations in most of the sentences which you have pointed out above.

Comments of Dr. Aaron Kopman (Reviewer 2):

The literature on sugammadex is now so massive that any review article about this drug must have limited goals. The Introduction Section ("Background" page 5) must explain that this review is focused on aspects of the clinical use of sugammadex that are controversial or may
require special attention. A brief outline of the topics to be covered at the outset would be very helpful.

Page 5, lines 2-9: This section needs a total rewrite. The sentence beginning "As sugammadex is most commonly..." is confusing and adds nothing of value to the introduction. Delete. Ditto the sentence mentioning "new opportunities and challenges." What opportunities? What challenges? Etc. Ditto, the comment re "best clinical practices." Most of this introduction is composed of elaborate language saying nothing. Keep it simple.

We have rewritten “Background” section, as suggested.

Sugammadex is now a well understood drug. Thus I question the necessity of including the section entitled "Characterizes and Clinical use of Sugammadex." (Page 5, line 13 thru Page 614). Delete.

We have deleted "Characteristics and Clinical use of Sugammadex." Section.

The Section on Recurrence of Neuromuscular Block (pages 7-8): This section should begin by noting that recurrence of block post sugammadex administration has been observed. Give examples. Only then should possible mechanisms be discussed.

We have modified this section based on your suggestion. In this section, we gave examples of recurrence of neuromuscular blockade first, and then discussed about the mechanisms.

While administering sugammadex based on actual body weight in the obese has been recommended, this may be unnecessarily expensive. Van Lanker (ref #69) suggest 140% of ideal body weight (IBW). Sanfillippo (ref # 70) argues that doses based on IBW may be adequate.

We moved this discussion to the “Sugammadex Use in the Obese Patient” section.

This section of the manuscript is meant to deal with the issue of recurarization however refs #s 7, 8, 9 and 13 do not deal with this occurrence. References 10-12 are more to the point. It should be noted that in refs 10 and 12 clearly inadequate doses of sugammadex were delivered and the degree of "recurarization" was modest indeed. Reference #11 is the only case I can find describing clinically serious recurarization post sugammadex. In fact this case is so unique that one must wonder if the intra-op neuromuscular monitoring (kinemyography) was accurate.

I must take issue with the authors' comment on page 8, line 14. Certainly, objective neuromuscular monitoring is optimal. Nevertheless, if the manufacturers' recommendations re sugammadex dosage are followed (dose based on TOF-count or post-tetanic count at the adductor pollicis) I see no reason why qualitative monitoring is not sufficient. It must be remembered that these doses were intended to work for vecuronium as well as rocuronium, a more difficult drug to reverse.
The authors will concede that qualitative monitoring might be sufficient in clinical practice. However, objective neuromuscular monitoring is ideal. Therefore, we have added the following statement: (ideally, objective neuromuscular monitoring)

Planned Re-establishment of Neuromuscular Blockade after Sugammadex Administration.


We have added the following references and statements:

“Sugammadex itself is not metabolized, and most of it will be excreted in urine unchanged. The rate of clearance of sugammadex is similar to the glomerular filtration rate, and its elimination half-life is approximately 100 minutes (Gijsenbergh et al., Kleijn et al.).”

Hypersensitivity/Allergy

Testing for and treatment of sugammadex induced allergy/anaphylaxis is no different from other allergens e.g. rocuronium. Hence, I'm not sure that lines 7 - 16 on page 13 are necessary.

We have deleted Figure 3 and added the following statement:

“Testing for and treatment of sugammadex-induced anaphylaxis are not different from those of other allergens.”

Bleeding Time Etc.

Put this in a historical perspective. Initial in vitro observations suggested that sugammadex in high doses mildly elevated the PT and APTT. Subsequent clinical studies have not confirmed that sugammadex is associated with any risk of peri-operative bleeding.

We have added the following statements:

“Although sugammadex increases some laboratory coagulation parameters, the use of sugammadex has not resulted in clinically significant postoperative bleeding.”

The Obese Patient
The statement (page 19, lines 8-9) that sugammadex should be dosed on actual not ideal body weight is not universally agreed upon. Yes, using actual body weight is the most conservative approach, certainly there are advocates of that approach (see ref #71), unfortunately this has potentially less than desirable economic consequences. There is considerable opinion that dosage of this magnitude is not required. See references #69 and 70. Loupec et al (ref #9) report that "In morbidly obese patients, 4 mg/kg of ideal body weight of sugammadex allows suitable reversal of deep rocuronium-induced neuromuscular blockade. Monitoring remains essential to detect residual curarisation or recurarization." Similarly Abd El-Rahman et al. [Comparison of three different doses sugammadex based on ideal body weight for reversal of moderate rocuronium-induced neuromuscular block in laparoscopic bariatric surgery. Minerva Anestesiol. 2017; 83:138-144] concluded that "sugammadex 1.5 mg/kg calculated according to IBW successfully reversed moderate rocuronium-induced neuromuscular block in laparoscopic bariatric surgeries." Finally, Badaoui et al [Reversal of neuromuscular blockade by sugammadex in laparoscopic bariatric surgery: In support of dose reduction. Anaesth Crit Care Pain Med. 2016; 35:25-9] suggest a dose based on IBW plus 35-50% quite similar to the recommendations of Van Lancker (ref #69).

Bottom line: This is still an area of controversy. If sugammadex were inexpensive opting to base doses on actual body weight would seem reasonable. At about $90 for a 200 mg vial acquisition costs must be a consideration.

The authors agree that dosing sugammadex on IBW vs TBW remains controversial and have adjusted the manuscript to reflect this. We have added the two references mentioned (Badaoui and Abd El-Rahman) as well to further describe the various issues.

We have maintained our recommendation to utilize TBW however call for more data by stating:

“Indeed, sugammadex dosing regimens remains controversial in the obese patient. If clinicians rely upon doses other than those based on IBW, the financial impact of administering more sugammadex must be considered. Furthermore, some literature suggests that using IBW-based dosing provides adequate neuromuscular blockade reversal. With these concepts in mind, the authors recommend a conservative approach of administering a dose of sugammadex that is based on the measured (objective) level of neuromuscular blockade and the TBW in obese patients, at least until more data become available regarding the safety and reliability of such dosing. This practice should reduce the risk of postoperative residual neuromuscular blockade in obese patients. Indeed, the risk of “overdosing” sugammadex is overshadowed by the risk of postoperative pulmonary complications from insufficient neuromuscular recovery in this vulnerable population.”

Renal Impairment:

What are the authors recommendations in ESRD. Do they recommend avoiding sugammadex? They never say.
We have edited this section to include the following recommendation:

“Utilizing sugammadex as reversal agent in patients with renal impairment appears to be a reasonable option, based on the available data, although large scale randomized controlled trials are still needed to establish efficacy and safety.”

Cost:

Page 25 line 15 thru page 26 line 3: It is true that that total paralysis time from rocuronium 1.2 mg/kg followed 3 min later by sugammadex 16 mg/kg is slightly shorter than the duration of effect of succinylcholine 1.0 mg/kg. To imply that this is "cost effective" makes defies logic. The proposition that reversal with sugammadex in CICV situations is a potential life-saver compared to succinylcholine has yet to be proven. In fact, a convincing argument can be made that "rescue reversal" is largely a myth. See Naguib et al. [The Myth of Rescue Reversal in "Can't Intubate, Can't Ventilate" Scenarios. Anesth Analg 2016: 123:82-92].

The authors are familiar with this important article and have added the reference and the following statement:

“Nonetheless, the CICV crisis should be managed by focusing on restoration of airway patency, oxygenation, and ventilation and not relying solely on pharmacologic rescue from neuromuscular blockade. (Naguib et al)”

Page 26, lines 5-7. This is not exactly what happened. Neostigmine was one of a large number of "grandfathered" drugs whose use anteceded the FDA approval process. About a decade ago, in an attempt to get some control over these compounds the FDA introduced a greatly accelerated and relatively inexpensive approval protocol for these old drugs. Eclat Pharmaceuticals took advantage of this process, received FDA approval, applied for and received a "brand name" and promptly raised the price of neostigmine by an order of magnitude. Once Eclat had FDA approval they then petitioned the FDA to remove all competing generic formulations from the drug distribution chain. The Agency complied.

Currently in the USA a case can be made that sugammadex reversal is cost competitive with neostigmine-glycopyrrolate. However, this is probably not true for much of the world where neostigmine remains quite inexpensive.

The authors agree that the cost of neostigmine in other parts of the world needs to be addressed and have added the following statements:

“If Japan and Italy, sugammadex can be as much as 20 to 40 times the cost of traditional reversal agent, such as neostigmine (Ministry of Health Japan., De Robertis et al.). Despite the cost difference between sugammadex and acetylcholinesterase inhibitors, Japan has a largest market share in the world because it has the reimbursement system in which additional costs can be charged directly to the patient (Schaller et al.).”
“However, neostigmine remains relatively cheap in many parts of the world and the difference in cost of these reversal drugs must be considered.”

Conclusions: Page 27, line 2. While it is hard to argue against the virtues of objective neuromuscular monitoring, in an environment in which sugammadex is readily available I would maintain that mandatory use of a conventional peripheral nerve stimulator is sufficient. Yes, the depth of neuromuscular block is necessary information if sugammadex is to be used rationally and safely. However, once the subjective TOF-count or post-tetanic count is known if the manufacturer's dose recommendations are followed, I would suspect that inadequate neuromuscular recovery must be very rare indeed.

The authors agree that qualitative monitoring is mostly sufficient in clinical practice. However, objective neuromuscular monitoring is ideal. Therefore, we have added the following statement: (ideally, objective neuromuscular monitoring)

Table 1. Delete.

We decided to keep Table 1 but delete “Hepatic Failure”, “Pediatrics”, and “Geriatrics” since they are not addressed in our manuscript.

List of Abbreviations: This should precede the Introduction.

Figure 3: None of this is unique to hypersensitivity to sugammadex. Delete.

We have deleted Figure 3.

We hope you find our manuscript suitable for publication and look forward to hearing from you.

Sincerely,

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