Reviewer’s report

Title: Three suspected cases of sugammadex-induced anaphylactic shock

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Reviewer: MARCEL VERCAUTEREN

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MAJOR COMMENTS

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.

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 admit that up to now most reported reactions were rather mild. Seems contradictory

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?

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)

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.

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

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?

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.

10. Case 2. Why was first phenylephrine given?

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

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 paCO2 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.

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.

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

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

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?

MINOR COMMENTS
Mostly concerns english language susceptible for improvement. To give few examples : case 1 : ... he had a fit of coughing ?? a strong possibility of bronchospasm ?? Before extubation ... sugammadex was administered : I would reverse the sentence : After the administration of .. sugammadex , the patient was extubated (although the conditions for extubation should be better precised !, see abvove).

**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:**

I received financial compensation from MSD (manufacturer of sugammadex) for consultancy meetings and expertise