Reviewer's report

Title: Three suspected cases of sugammadex-induced anaphylactic shock

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Reviewer: Lene Heise Garvey

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General comments

The authors describe 3 cases of perioperative allergic reactions attributed to sugammadex. The cases are relatively well described and patients have subsequently undergone skin testing, which was concluded to be positive to sugammadex. 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.

Eventhough 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.

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’es 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.

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.

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.

Specific comments.

Abstract
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.

Background
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
Page 4 lines 4-8 The description of the mechanism of action of Sugammadex should be made shorter and clearer.
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.
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.
Page 6 line 4 In theory rocuronium should not work just after the administration of Sugammadex – pleas comment on this.
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 Krøigaard 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
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.
Page 9 line 12 -15 please elaborate on the halflife of tryptase making it possible to sample tryptase 1-2 hours after a reaction.
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?

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.

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.

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

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

Work on advisory board for MSD, USA