Author’s response to reviews

Title: Population pharmacokinetic-pharmacodynamic model of propofol in adolescents undergoing scoliosis surgery with intraoperative wake-up test: a study using Bispectral Index and composite Auditory Evoked Potentials as pharmacodynamic endpoints

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Nieuwegein, November 13th 2018

Dear Professor Kazocha,

On behalf of the authors I would like to thank you and the referees for the review of our manuscript entitled ‘Population pharmacokinetic-pharmacodynamic model of propofol in adolescents undergoing scoliosis surgery with intraoperative wake-up test: a study using Bispectral Index and composite Auditory Evoked Potentials as pharmacodynamic endpoints’.
In this letter we provide a point-by-point response to the reviewers comments. In the revised version of the manuscript, all changes are indicated in the text using track changes.

Mustafa Said Aydogan (Reviewer 1):
Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.
Thank you for reviewing our manuscript.

Tobias Piegeler, M.D. (Reviewer 2):
In their manuscript, entitled "Population pharmacokinetic-pharmacodynamic model of propofol in adolescents undergoing scoliosis surgery with intraoperative wake-up test: a study using Bispectral Index and composite Auditory Evoked Potentials as pharmacodynamic endpoints" the authors are reporting a new PK-PD model for propofol in adolescents derived from data obtained from a small clinical study in patients undergoing scoliosis surgery. The overall idea of the study is interesting and the manuscript is well-written. The presentation of the results and the discussion is extensive and puts the results very well into context. However, there are some issues, which I would like the authors to address:

1. Awareness & pain: The authors discuss results from their own previous study (Ref. 29), in which they have tested a similar group of patients regarding a possible recall or sensation of pain during the wake-up test. Did the authors also do this for this particular study?

For this particular study patients were asked whether they had a possible recall or sensation of pain during the wake-up test. The results from this study have been published in another article. Because of this misinterpretation we have adjusted this part of the discussion as it is apparently not clear that both studies were done in the same patient group.

2. Due to the fact that I am just a clinician-scientist anesthesiologist, and not a specialist in statistical or pharmacologic models, unfortunately I am not able to fully assess and comprehend the quality of the presented calculations. However, in order to increase the appeal of the manuscript to a broader audience of anesthesiologists, i.e. the readers of BMC Anesthesiology, in my opinion the authors should aim at the following things:

   a. Streamline the discussion.

   b. Explain not only your model better but also its implication into daily practice: Possible topics might be:

      i. Why might this model be important?
      ii. Will it be applicable, e.g., in a new form of infusion pump?
      iii. How does it improve daily clinical practice?
      iv. Did the authors already change anything in their daily practice because of these results?
      v. […]

Thank you for this remark upon which we have revised the discussion and have added an extra
paragraph to our discussion which addresses the clinical impact of this study to the daily anesthetic practice.

We thank you for considering our paper to be published in BMC Anesthesiology and look forward to your response.

On behalf of all authors,

Yours sincerely,

Dr. H.J. Blussé van Oud-Alblas