Author's response to reviews

Title: Evaluation of propofol anesthesia in morbidly obese children and adolescents

Authors:

Vidya Chidambaran (vidya.chidambaran@cchmc.org)
Senthilkumar Sadhasivam (senthilkumar.sadhasivam@cchmc.org)
Jeroen Diepstraten (j.diepstraten@antoniusziekenhuis.nl)
Hope Esslinger (hope.esslinger@cchmc.org)
Shareen Cox (shareen.cox@cchmc.org)
Paul Samuels (paul.samuels@cchmc.org)
Thomas Inge (thomas.inge@cchmc.org)
Beverly M Schnell (schnell_beverly_martinez@lilly.com)
Alexander A Vinks (sander.vinks@cchmc.org)
Catherijne Knibbe (c.knibbe@antoniusziekenhuis.nl)

Version: 2 Date: 28 December 2012

Author's response to reviews: see over
Tom Rowles PhD  
Executive Editor  
BMC Complementary and Alternative Medicine

Dear editor,

Thanks for your consideration of our manuscript for publication in your journal. Please find our responses below:

**Re: Response to editorial comments:**
- Thank you offering to forward us a copy of your Clinical Pharmacokinetics paper. We would be very interested in assessing this previous publication, and its relation to your current submission.

As requested by you, we have submitted the published journal paper describing pharmacokinetics of propofol in this study population herewith for your perusal. Reference to the same is “Diepstraten J, Chidambaran V, Sadhasivam S, Esslinger H, Cox S, Inge T, Knibbe CAJ, Vinks AA (2012). Population pharmacokinetic modeling of propofol in morbidly obese children and adolescents. Clin Pharmacokinet 2012; 51 (8): 543-551”. We would also like to bring to your attention that there is no duplication of results or conclusions. In the already published paper, none of the details regarding hemodynamics, dosing or respiratory adverse events have been discussed and hence there is no overlap with present submitted manuscript. We feel that relevance of the clinical message that we relay here is important. At this point, we have not completed PD analysis for this study due to insufficiency of data recorded for that purpose. This will be our goal in the future.

- Please include Authors’ Contributions and Competing Interests sections in your manuscript

We have added the sections you have requested.

**Re: Response to reviewers’ comments**
We greatly appreciate the reviews and valuable comments of the reviewers. We have revised the title, the manuscript and figure 1 in accordance with the comments / suggestions of the reviewers, and addressed their comments point-by point (see bulleted points below). Please note that the revisions in the text of the manuscript are in red colored font.

Sincerely,

Vidya
Reviewer 1  
Title: Evaluation of propofol anesthesia in morbidly obese adolescents  
Version: 1 Date: 31 October 2012  
Reviewer: Frederique Servin

Thanks much for your review and comments.

Reviewers report:  
Owing to the growing number of patients involved, the manuscript entitled “Evaluation of Propofol Anesthesia in Morbidly Obese Adolescents” corresponds to a very real concern in today anesthesia. The title is slightly misleading in that not only adolescents but also children have been included in this prospective descriptive study. This is an important point since Rigouzzo et al (Anesthesiology 2012) have demonstrated that puberty induced changes in the pharmacology of propofol.

Since the age of the children recruited ranges from 9 to 18, we agree with your comment and have changed the title to reflect that children were also included.

The authors have carefully described their anesthesia technique, resulting in an important overdose of propofol. This overdose, obvious from the BIS values to which the anesthetist had no access, resulted in a delayed recovery, with a significant number of respiratory adverse events.

It is a well known fact that titration of propofol to hemodynamic effects is very difficult, not to say useless. Here propofol was the main anesthetic agent, with only small doses of opioids, because fentanyl tends to accumulate and higher doses of this agent would result in even more respiratory events. This is the reason why, specifically in obese patients, remifentanil is nowadays considered as the best agent. With higher opioid concentrations, it allows a significant reduction in propofol doses. This reduction in propofol doses is not due to an effect on the hypnotic component of anesthesia, but to the fact that remifentanil rather than propofol blunts the response to adrenergic stimuli.

We agree with your comments that the use of remifentanil could reduce the amount of propofol used. Our reasoning for not using remifentanil is because in our practice, we generally use fentanyl and morphine, instead of short acting remifentanil infusions, in an effort to prevent development of opioid hyperalgesia and having to use more opioids in the postoperative period (due to increased pain after remifentanil is stopped) (Angst 2006). We did not use remifentanil in this study so that it would be reflective of clinical practice.

There should be a significant paragraph in the discussion as to whether the propofol overdose is due to the fact that the patients were obese, or to the fact that the patients were children. What are the real requirements in propofol in the adolescent, obese or not? Which concentrations are required to maintain anesthesia in this population?
Thank you for raising these important questions. Since children generally require higher propofol concentrations compared to adults and have a higher EC50 (Rigouzzo 2008), we do not believe the overdose was because they were children. In fact, there are few reports in children suggesting that children are either less sensitive or equally sensitive to the anesthetic effects of propofol, compared to adults (Munoz 2004). Concentrations of 4.3±1.1 mg.l⁻¹ have been reported to correlate with BIS of 50 in children (Rigouzzo, 2010), while the concentrations we observed were much higher (The mean (SD)(number of samples) for propofol concentrations collected during 15-30, 30-60, 60-90, 90-120 and >120 minute time intervals of maintenance anesthesia were 6.8(1.8)(26), 6.9(2.5)(41), 5.8(2.2)(36), 5.4(2.7)(15) and 6.1(3.2)(29) mg.l⁻¹ respectively, as shown in Figure 4A). There are no reported ideal propofol concentrations for maintenance of anesthesia in obese adolescents in literature, as far as we know.

The authors have measured propofol concentrations in quite a few samples, but they don’t really use this information. Looking at the literature, I realize that this part of the study was used in another paper (Clin Pharmacokinet. 2012 Aug 1;51(8):543-51). The authors should have said so, specifically since they have shown that in those children, propofol dosage during maintenance should be calculated on TBW, exactly as in adults. This could be linked to the papers from La Colla, Albertin et al on validation of propofol PK models for TCI in the obese. It seems that in those adolescents, TCI with the Marsh model might be a good solution.

We have referenced in the revised version the published paper wherein PK analysis has been described already. While we were preparing this manuscript, the PK analysis had not been complete. The aim of this paper is also not to discuss PK-PD analysis of propofol but to highlight importance of monitoring BIS, and like you have mentioned, the difficulty in using hemodynamic parameters to titrate propofol in this population. We have not included a PK discussion in this article as we do not describe PK analysis of propofol in this manuscript.

For induction though, quite a few data are showing up in the literature, demonstrating that propofol dose should be estimated on LBM rather than TBW. It seems that obese children are no different (Anesth Analg. 2012 Jul;115(1):147-53).

True, and we saw the same correlations on linear regression of LBW and Induction dose, which had better correlation than with total body weight. We have depicted that in revised Figure 1, but this requires larger prospective studies and a formal PKPD analysis to be confirmed.

To conclude, I would say that this is a descriptive study on current practice in the USA were TCI is not available, and its real interest would be enhanced by a
significantly improved discussion.

We have made modifications in the discussion to reflect the clinical aspects that we report in this manuscript.

PS: despite being a TIVA/TCI addict, I use desflurane + remifentanil in my (adult) MO patients …

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

Thanks you for recognizing the relevance of this article.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer 2

Title: Evaluation of propofol anesthesia in morbidly obese adolescents
Version: 1 Date: 5 November 2012
Reviewer: Bruce Green
Reviewer's report:
Thank you for inviting me to review the manuscript entitled "Evaluation of Propofol Anesthesia in Morbidly Obese Adolescents". The manuscript evaluates an important clinical problem of how to dose propofol in obese adolescents and is observational in nature.

Thank you for review and valuable comments.

Major Comments
I have several major comments. The clinical problem of how to dose obese patients is well understood. What seems less well understood is how to design a clinical trial that allows useful analyses to answer the question. Understanding PK-PD relationships across body size in PK-PD requires a design across a range of subjects, from normal through to obese. This study does not have any normal weighted subjects included in design, hence determining an answer to the question is challenged and the manuscripts validity questionable. On that point, there is no real attempt to answer the question, so I am unsure how this helps clinicians?

This report is a descriptive analysis of the clinical use of propofol in morbidly obese children and adolescents and the problems it poses. We would like to emphasize through our findings that dosing propofol on the basis of clinical parameters in this sub-group of population is challenging and requires improved monitoring to reduce the side effects, in the absence of dosing guidelines.

Finally, some of the authors have published quite sophisticated analyses of similar data in the adult population. Why was this approach not taken here? The descriptive approach here cannot help prescribers identify a suitable dose. Surely it would be more scientifically advisable to combine data from normal and obese adults, create a super-dataset and then work out the appropriate dosing regimen for obese children using simulation techniques?

We have completed pharmacokinetic analysis of the propofol data obtained in this study and the results have been published (Diepstraten J, Chidambaran V, Sadhasivam S, Esslinger H, Cox S, Inge T, Knibbe CAJ, Vinks AA (2012). Population pharmacokinetic modeling of propofol in morbidly obese children and adolescents. Clin Pharmacokinet 2012; 51 (8): 543-551). The data we had collected, especially the blood sampling/BIS recording in the first 10 minutes of propofol anesthesia was found inadequate to do a formal PK PD analysis. A formal PK-PD analysis after collection of more data and recruitment of more patients is our goal for future analysis.
We agree with your comments regarding the validity of Servin’s formula in children as it was used in adults. That is the issue with clinical dosing in that we do not have an evidence based scalar for dosing propofol in the morbidly obese child/adolescent. We used adjusted body weight as it has been used by Servin without evidence for propofol accumulation. In Servin’s formula, the input IBW is given by the formula 22*(Height)$^2$, where 22 kg/m$^2$ represents ideal BMI for adults. Since ideal BMI is not necessarily 22kg/m$^2$ in adolescents, we used American Association of Pediatrics recommended definition of ideal BMI as 50$^{th}$ percentile for that age and gender, derived from CDC charts (as mentioned in revised methods).

We do not believe using ABW was the reason for propofol overdose. Our PK analysis does indicate that clearance is correlated with total body weight non-linearly (allometric relationship), which has been found in other studies also (Van Kralingen 2012, Cortinez 2010). These studies recommend use of TBW for maintenance dosing. The scalar ABW is smaller than TBW and even LBW Lean body mass (calculated for each child as suggested by Peters 2011). Hence we believe the use of the scalar ABW for dosing is not the cause of the over-dose.

2) Figure 1 is problematic. It is better to look at bias and precision between the size descriptors. As mentioned above, why exclude normal weighted subjects in the analysis? Also, why assume it is a linear relationship and report an r value? Typically the axes are ask the other way round with dose on the y and Weight on the x axis to allow identification of non-linear relationships.

Thanks much for your excellent suggestion. Based on your recommendation, we have switched the axes around for Figure 1. We tested for linear, quadratic and cubic trend but only linear trend is significant. We have added root mean square errors and the fitted regression lines in the revised plot. The relevance of this plot will not be over stressed as it needs to be confirmed by a formal PK PD analysis as well as larger prospective studies.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer 3

**Title:** Evaluation of propofol anesthesia in morbidly obese adolescents  
**Version:** 1  
**Date:** 18 November 2012  
**Reviewer:** Hendrikus Lemmens  

**Reviewer's report:**

**Major Compulsory Revisions:**

Experienced clinicians know that propofol titrated to the infusion rates and durations as described in this study will result in delayed emergence not only in obese patients but also in the normal weight population. The rapid offset of action of propofol as mentioned in the first sentence of the introduction does not apply to the clinical scenario of this study. Nevertheless, this is an important and clinically relevant study.

Thanks for your review and comments regarding the relevance of the study.

Regarding the design, specifically the choice between propofol up titration or administration of fentanyl at signs of inadequate anesthesia seems arbitrary. Please comment on this issue.

We have attempted to improve the clarity of the design in Methods. Since it is in general difficult to know for certain whether it is pain or inadequate anesthesia causing hemodynamic changes, we have explained that whenever the change occurred after increased painful stimulation, it was considered requirement for opioid rather than increase in propofol rates. Propofol rates were decreased when the BP/HR were lower as this is mostly due to the hemodynamic effects of propofol and depth of anesthesia.

In this report only mean propofol concentrations during maintenance and emergence of anesthesia are mentioned. However, blood samples for propofol concentration determination are taken at intervals that seem specifically designed to characterize the pharmacokinetics of propofol. Together with the wealth of clinical effect parameters and the BIS data a full population pharmacokinetic/pharmacodynamic model can be developed which one of the authors is “expertly” and perfectly able to perform. In my view, it is not a good practice to split up the results of one study in different papers.

Your comment is absolutely correct. The PK analysis has been published elsewhere (Diepstraten, 2012). The data we had especially the blood sampling/BIS recording was found inadequate in the first 10 minutes of anesthesia to do a formal PK PD analysis at the time. Since then, we have recruited more patients for a formal PK PD analysis, which is our future goal.

Reference 23 is incorrect.

Thank you for pointing that out. Reference 23 has been corrected.
Servin (reference 14) never mentioned the IBW equation as mentioned under study protocol in the methods.

Servin’s formula is for morbidly obese adults, but ideal BMI for adolescents is not necessarily 22 kg/m². In Servin’s formula, the input IBW is given by the formula 22*(Height)², where 22 kg/m² represents ideal BMI for adults. Since ideal BMI is not necessarily 22kg/m² in adolescents, we used American Association of Pediatrics recommended definition of ideal BMI as 50th percentile for that age and gender, derived from CDC charts (as mentioned in revised methods).

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

Thanks for acknowledging the relevance of this study.

**Quality of written English:** Acceptable

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