Reviewer's report

Title: Human Physiologically Based Pharmacokinetic Model for Propofol: I) Description and validation of model.

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Reviewer: Richard Neil Upton

Reviewer's report:

General
I agree with the authors that there is a need to explore physiologically based approaches to modelling the pharmacokinetics of propofol. Much of the variability in the kinetics of propofol in clinical use is likely to be due to the physiological differences between patients that are inherent in differences in their size, shape, cardiovascular status and underlying disease.

The concept of predicting propofol distribution volumes in tissues from their lipid content (and the free fraction in blood) is intriguing, and will be very useful if supported by experimental evidence. However, I feel that the current model as proposed by the authors has not been critically reconciled with the propofol literature. While the model does provide a reasonable fit to a subset of the arterial plasma concentration data of Schnider, a good fit of these data is not proof that all the underlying assumptions of the model are correct. There are many parameters sets for the model that could fit these data (which essentially reveals 3 underlying exponentials), not all of them will be correct. In an ideal world, I would like to see concentration data collected in other sites in the body used to develop the model (especially concentration gradients across the lungs). In reality, such data sets are hard to come by, but there are key papers in the literature that are at odds with the proposed model. This becomes important when predictions are made from the model. There are undoubtedly some useful insights that can be made using this approach, particularly with respect to the effect of elution from fat on the terminal half-life of propofol. I encourage the authors to continue to refine their model.

At this stage I have not checked the details of the equations presented in the paper, but they seem broadly consistent with what I would expect.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. A concept of lung sequestration (time constant of 80 min) for a fraction of the bolus dose (but not the infusion dose is novel) is used, and a mechanism is proposed based on trapping of the lipid vehicle in the lungs. However, this is not consistent with the literature. The paper of He et al. quoted by the authors suggests a FIRST-PASS extraction of about 28% - this is only the amount of the injected propofol dose that hasn't left the lungs by the time the ICG has emerged. This missing propofol emerges a short time latter and is evident in Fig. 1 of He et al - their estimate of the apparent lung distribution volume of propofol is 2.52 L, which is in agreement with the small pulmonary artery - arterial difference shown in their infusion study. What do the authors make of the study of Dawidowicz et al. (Anesthesiology 2000; 93: 992-7) which shows the production of a propofol metabolite across the lungs of man, but only a small concentration gradient across the lungs? Sequestration of 20-40% of the dose across the lungs would produce very large concentration differences across the lungs. In my own studies using sheep, we have found the apparent lung volume of propofol to be small (about 2.5 L), with a non-linear extraction term need to
explain the dose dependency. Although we believe sheep differ from man with respect to this metabolism, we have seen no evidence of sequestration of the magnitude proposed by the authors.

2. Wouldn't the lung sequestration produce non-linear kinetics? There are many studies, including Schnider's original work that support linear kinetics for propofol in man.

3. By what mechanism is the lung sequestration proposed to reduce with age?

4. I agree with the authors that a limitation of their model is that it doesn't account for the blood flow changes produced by propofol - the most import of these may be that propofol reduces cerebral blood flow by up to 50%, and therefore changes kinetics in its most important target organ.

5. Propofol kinetics are not altered greatly by obesity (Servin, Anesthesiology 1993; 78: 657-65) - how can this be reconciled with the central role of fat uptake in their model?

6. The authors are not correct in that Ludbrook and Upton advocated a flow-limited well mixed model for propofol in the brain - we found the best fit to be a model with partial membrane limitation (Upton & Ludbrook, Br J Anaesth 1997; 79: 497-504). With respect to skeletal muscle, we found propofol kinetics to substantially deviate from flow limited kinetics (Zheng et al. Xenobiotica 30: 1079-1090 (2000)). Therefore, data for two tissues (at least in sheep) are not consistent with the underlying assumption of flow limited kinetics used in the model.

7. The paper uses symbols and terminology that deviate from standard pharmacokinetic practice, which I presume is because the first author comes from a physiological background. Standardising the symbols and terminology these would greatly help the readers of this paper, which are likely to have a pharmacokinetic background. For example, the fractional clearance (Eq 10) is known as the hepatic extraction ratio, the liver metabolic constant is known as the intrinsic clearance. With respect to symbols, I use Council of Biology Editors. Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers. 6th ed. New York, NY: Cambridge University Press; 1994.

8. Allowing for a period of mixing before the first sample is taken is common for compartmental modelling. However, it is unreasonable to ignore the data before 2 min in a physiological model, which should hopefully give a reasonable account for vascular transport and lung kinetics. Most patients given a bolus of propofol are asleep before 2 min has expired, so it is important to model this period well. Conversely, if the 600 min data was considered less important, what weighting scheme was applied to prevent this data point skewing the fit? Was the CV of the pooled data at 600 min larger than the other time points, suggesting the need for such a weighting scheme?

9. The objective function (described as "weighted residual" on page 9) used is very unusual - what is it's origin? It incorporates 1/y weighting by default, and uses absolute values rather than a square term to deal with negative residuals. It uses an average rather than a sum of residuals. Readers are likely to be suspicious of this different approach unless its behaviour is documented, and its use if justified. Furthermore, no standard deviations for parameter estimates (calculated from the Hessian matrix) are given. These are essential for the reader to have confidence in the precision of the parameter estimates, and are a useful tool for testing for underdetermined models where there is not enough information in the data to estimate all models parameters uniquely.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I have been working on a physiologically based recirculatory model of propofol kinetics and dynamics in man that was near completion when I received this paper to review.

A slightly different approach to what is presented here, and I view the two approaches as complimentary.

I have no financial conflicts of interest.