Author's response to reviews

Title: Human Physiologically Based Pharmacokinetic Model for Propofol

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Author's response to reviews: see over
Response to referees' comments:

General comments and major changes:

We wish to thank the referees for their careful, thorough and critical evaluation of these manuscripts. We feel fortunate that investigators that have such extensive experience in the field of propofol pharmacokinetics were willing to take the time and effort required for this review. In general, we agree with the reviewers' criticisms and have modified the revised manuscript to satisfy them. Below, we have listed each of the specific comments of the reviewers, along with our detailed response and list of changes (in italics).

We have made two major changes in the revision.

1) As suggested by the referees and by the editor, we have withdrawn the second paper ("Clinical and Physiological Implications").

2) We have added one section to the Discussion: - a discussion of the influence of obesity on the pharmacokinetics.

Referee 1.

Major Compulsory Revisions:

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 later 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.

The referee raises an important issue - how to interpret the experiments of He et. al which they interpreted in terms of 28% sequestration. We have also been concerned about this issue. The problem is that because of the large difference in the volume of distribution between ICG and propofol, the first pass outflow curves from the lung will be significantly different, even if there is no sequestration. Ideally, if there were no recirculation, then the propofol sequestration would be equal to:

\[ F_{pul} = 1 - \frac{AUC'_{propofol}}{AUC'_{ICG}} \]
where AUC' is the dose corrected AUC. This is identical to He et. al. eq. 6 if $\tau = \infty$. However, because of recirculation, one must stop the integration over the concentration before recirculation alters the result. It is not clear how He et. al. actually determined the value of 28%. We have recalculated the value from their published fig. 1. In the methods, they say they integrate up to the time when ICG recirculation becomes important - about 30 seconds. However, using this time we found an extraction value of about 40%. Another possibility is to integrate for different times for ICG and propofol - using a longer time for propofol because of its larger volume of distribution. If one uses a $\tau = 30$ sec for ICG and 45 seconds for propofol, one finds an extraction of about 16%. However, this must surely be an underestimate of extraction because there is obviously significant propofol recirculation during the time from 30 to 45 seconds. A third possibility is based on the observation that the propofol concentration seems to level out at about 50 sec and to assume that this represents the background recirculation level over the last 10 seconds and to subtract it out - which yields a sequestration value of 25%, close to the value reported by He et. al. It should be emphasized that all these estimates are for total sequestration - with no release during the time of the integration. The propofol concentration is greater than the ICG concentration during the 20 to 30 second time period because of the differences in their volume of distribution (and the corresponding mean transit time (see eq. 6, He et. al). Our estimate of the release time constant of 80 minutes is much longer than the He et. al. measurement period - and would not change the interpretation of the results of He et. al.

The measurements of Zauner et. al of Intralipid pulmonary A-V differences provide direct evidence about the release rate. At the highest infusions rates they find a sequestration of about 20%. When they stop the infusion, they find a release of the sequestered Intralipid that has a time constant of at least 15 minutes.

Clearly, both of these experimental measurements have their limitations, but they are roughly consistent with our interpretation of pulmonary sequestration.

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?

We had ignored this paper. We have now addressed this issue by adding the following paragraph to the Discussion section.

It has been assumed in the PBPK model that there is no pulmonary propofol metabolism. This is supported by the experiments of He et. al. [35] who found no significant pulmonary artery - radial artery propofol concentration difference during a constant infusion. Also, Gray et. al.[32] found no arterial - venous difference in propofol or propofol metabolites during the anhepatic phase of liver transplantation. However, in opposition to these experiments, Dawidowicz et. al. [39] found a significant pulmonary arterial - venous difference for both propofol and propofol metabolites, indicating some pulmonary metabolism.
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.

   *We assume that the referee is referring to the fact that the fraction sequestered might depend on the dose. However, since the total amount sequestered is only 20 to 30% for most young subjects and the dose dependence is really not known, this would be a relatively small effect that would be difficult to detect.*

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

   *We have no idea. We have added the following two sentences to the revised version.*

   The lack of sequestration in the oldest subjects might be explained, in part, because they received only half the bolus dose of the other two groups. The difference between the young and middle-aged subjects is a surprising result and one that clearly requires further documentation.

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 important of these may be that propofol reduces cerebral blood flow by up to 50%, and therefore changes kinetics in its most important target organ.

   *Because of this variation and other uncertainty about brain/blood partition, we have removed all reference to brain concentration from the revised version.*

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?

   *This issue is now directly addressed in the Discussion with a new section comparing normal and morbidly obese subjects. In the paper of Servin et. al., the washout was only followed for about 8 hours after the end of the infusion. Because of the very long time constant of the adipose tissue (about 33 hours, see Discussion), this 8 hour period is not long enough for the differences in the adipose tissue fraction of obese subjects to make a dramatic difference. This is illustrated in the new fig. 14 of the revised version.*

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.
Our statement was based on the following calculation using the data from the paper by Ludbrook, Upton, Grant and Martinez ("Prolonged disequilibrium between blood and brain concentrations of propofol during infusion in sheep", Acta Anesth. Scand. 1999; 43: 206). At equilibrium, they found a brain concentration of 5 ug/ml and arterial concentration of 1.5 ug/ml (Ludbrook et. al. fig. 1), corresponding to a brain/blood partition of 3.33. Using their estimates of brain mass (75 gm) and brain blood flow (40/ml/min) - the time constant for the well mixed, flow limited brain would be 6.2 minute (=75*3.33/40). Ludbrook et. al. also determined the half time for brain uptake of 3.52 minutes (p. 209) and previous estimates of 3.5-7 min. This corresponds to a time constant of 5 to 8 min - in good agreement with the flow limited well mixed model time constant of 6 minutes. The referee is correct that they do not specifically state that the brain is well mixed. We have modified this sentence in the revised version:

"Based on direct measurements of arterial, venous and brain propofol concentrations during infusions in sheep, the time constant for brain uptake is consistent with a flow limited, well mixed model [31]."

We specifically referred to this paper because it seems to provide the most direct experimental support for the well-mixed model. We feel that the interpretation of the experiments of Zheng et. al. is complicated by the fact that venous blood is sampled from the femoral vein, and therefore has some components from skin, adipose and connective tissue and does not represent a single tissue compartment. The experimentally induced changes in femoral artery blood flow may change the relative fraction contributed by the different tissue. In the revised version we have now specifically sited this paper as an indication of the possible invalidity of our model assumption:

"This well-mixed tissue assumption is only correct as a first approximation and there is some evidence that it may not be rigorously correct for muscle [32]."

8. Allowing for a period of mixing before the first sample is taken is common for compartmental modeling. 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 a such a weighting scheme?

Accurate modeling of the data at 1 minute requires a much more complicated model with many more physiological variables. We have now included a reference to a paper by Mapleson et. al. that attempts to do this. The reviewer is correct that, in some cases, this may be clinically important; it is just not the goal of the current paper. No special weighting was applied to the time point at 600 minutes.
9. The objective function (described as "weighted residual" on page 9) used is very unusual - what is its 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.

The absolute weighted error is a standard statistical approach and is an option in most statistical packages (e.g. Sigmaplot). In X-ray crystallography (the background of D.G.L.) the standard function that is minimized is the "R factor" which is absolute weighted residual of the amplitudes. The absolute weighted residual has the major advantage over squared weighting in that it places less weight on outliers. In PKQuest the user can select either absolute or squared weighting, with or without a noise correction. The most important reason for using this form of the weighted error in this paper is that this was the form of the quality of fit reported by Schnider et. al, and we wanted to directly compare the PBPK and compartmental results. We agree that calculations of SE of parameter estimates would be useful. The current version of PKQuest does not include this. It is on my (D.G.L.) list of future modifications.
Referee 2.

General:
The authors note that they require only 2 parameters for fitting the data while NONMEM required 6 parameters for the same data set. This is not accurate; in the fitting process with PKQuest many (physiologic) parameters are present but have been "fixed". In other words, the author have taken best estimate of parameters from the literature for physiologic numbers and incorporated them in the model. They have not been called parameters only because the PKQuest program has not been allowed to optimize them to best fit the data. This requires assumptions about constancy of these parameters between subjects and between solutes.

In the revision, we have tried to consistently distinguish between "model parameters" (tissue blood flows, etc.) and "adjustable parameters". The point we are trying to emphasize is the quality of the PBPK model vs. the NONMEM compartment model as a function of the number of adjustable parameters. We hope that it is clear from the paper that none of the non-adjustable model parameters were adjusted in any way to improve the fit. They are exactly the same values that have been used in previous applications of PKQuest. We have tried to emphasize this in the revision.

Specific:
1) The author notes for Figure 3 that 60% of the bolus is sequestered but it is not clear from the manuscript how this number was derived or optimized.

The procedure that was used is now described in the first paragraph in the Determination of PBPK parameters section.

2) In table IV, the authors present data based on age. It is unclear if the values are significantly different by age. If not, they could be incorporated into a single value or else the significance should be established.

Although the statistical significance of the differences were small ($p \approx 0.05 - 0.1$), the use of the linear age correlations (eq. 13) did provide a better prediction (i.e, lower value of average weighted residual.)
The authors state that propofol is highly concentrated in the adipose tissue, a notion which to my knowledge is not entirely supported by the literature. The paper by Weaver et al on tissue/blood and tissue/water partition coefficients for propofol has not studied adipose tissue. The number which the authors of this paper refer to as an oil/water coefficient for propofol is a triglyceride/water partition coefficient in blood, the triglyceride being part of the micelli in the solvent of propofol for Diprivan, and I am not convinced this can be extrapolated to the physiological adipose tissue. The same can be said of the second reference quoted by the authors by Tonner et al, Anesthesiology 1992.

The reviewer is correct that this is major and central assumption of our model. There are two different experimental measurements that support our value for the Koil (lipid/water partition coefficient). The first is that of Weaver et. al who determined the partition of propofol between the lipid in Diprivan and water and found a Koil of 4715. (This is not the "triglyceride/water partition coefficient in blood" as stated by the reviewer). Since the Diprivan lipid is primarily soybean oil and egg lecithin (i.e. triglycerides) it is the best possible experimental model for adipose tissue - and the one we selected to use. In the PBPK literature it is common to use the octanol/water partition as an approximation to the physiological lipid/water (usually because the triglyceride/water value is not available). For propofol they give very similar results. We quote the value of Tonner et. al. 4300. We have also now quoted another estimate of the octanol/water value- 6165 reported by Hansch et. al. which seems to be the standard reference in the tabulated databases. (The PDR states an even larger value of 6761, but does not give a reference.) I personally contacted Dr. Weaver about his measurements and I am convinced they were very carefully performed. Triglycerides (eg. olive oil, soybean oil, lecithin) are generally considered the best possible model for biological adipose (fat) tissue. In the large tabulation of anesthetic solubilities by Stewart et. al. (Brit. J. Anaeth. 1973, 45: 282), the oil and fat tissue partition values are in nearly perfect agreement, if one corrects for the approximately 20% water in fat tissue. We have slightly modified the discussion of the choice of Koil in the revised manuscript:

"The value used for Koil of propofol was 4715, which was determined by Weaver et. al. [1] from measurements of the water/Diprivan partition and the triglyceride concentration in Diprivan. This is similar to the value of the octanol/water partition of 4300 determined by Tonner et. al. [19] and smaller than the octanol/water partition of 6165 reported by Hansch et. al. [20]. Triglyceride should provide the best model for tissue lipid/water partition."

Human pharmacokinetic studies of propofol in obese patients (Servin, Anesthesiology 1993) have demonstrated that the volume of distribution of propofol in morbidly obese patients was proportional to total body weight but there was no indication of a concentration of propofol in fat. The authors therefore need to strengthen their case if they want us to comply to their initial hypothesis. This is a
very important point since the authors rely on this hypothesis to support all their subsequent calculation.

In the revised version we have added a new section ("Physiological implications - body fat fraction:") to the Discussion section that specifically focuses on the pharmacokinetics of obese subjects and discusses the paper by Servin et. al. In the paper of Servin et. al., the washout was only followed for about 8 hours after the end of the infusion. Because of the very long time constant of the adipose tissue (about 33 hours, see Discussion section of revised manuscript), this 8 hour period is not long enough for the differences in the adipose tissue amount in obese subjects to make a dramatic difference in pharmacokinetics. This is illustrated in the new fig. 14 of the revised version.

The extrahepatic metabolism of propofol is quoted by the authors, but the way they handle it confuses me: in one subject, to fit the data, they attribute 10% of propofol metabolism to the kidney. Why is this subject different? Why the kidney since other organs, including fat, can conjugate xenobiotics?

Because there was only 1 subject out of the 24 that needed an extrahepatic term, we did not feel it was worth a detailed discussion. It is possible that this subject had a 20% higher liver blood flow than we assumed, and this could also account for the kinetics. The model is not very sensitive to where the extra metabolism occurs. In the revised MS we now state: "(about 10%, assigned arbitrarily to the kidney)" and have added the word "arbitrarily" to indicate that we do not have any good experimental support for this assignment.

Another problem is the hemodynamic effect of propofol. It does not induce a major drop in cardiac output, but through modulation of the sympathetic tone, it may modify the repartition of this blood flow to different organs (Piriou, Eur J Anaesth 1999). This is probably the reason why recovery is usually associated with a rebound increase in propofol blood concentration (Servin, Anesthesiology 2003). The effect of anesthetic drugs on cerebral blood flow is even more complex. Induction of anesthesia with thiopentone is associated with a reduction in cerebral oxygen consumption and cerebral blood flow (Bjorkman Acta Anaesthesiol Scand 1994), and propofol is probably not different. All this explains why, in order to improve pharmacokinetic modelling in anesthesia, specifically at induction of anesthesia (Kazama, Anesthesiology 2003), another approach currently favored is recirculatory modelling (Avram Anesthesiology 2003). All this does not reduce the interest of “static” physiological modelling, but I feel that the discussion would be much improved if these difficulties were analysed.

Because of this uncertainty in the actual brain blood flow, along with other questions about the brain/blood partition raised by the reviewers, we have completely removed any reference to brain concentration or pharmacodynamic effects from the revised manuscript. It is really peripheral to the main emphasis of this paper, which is on the prediction of the pharmacokinetics. The discussion of the pharmacodynamics would require another paper.
II) Clinical and physiological implications This part is on my opinion a bit premature, and I am not convinced by the authors extrapolation of effect site concentration through calculated brain concentrations mainly for the reasons quoted in the first part. So far, the theoretical effect site concentration defined through pharmacodynamic measures seems to give as good results without possibly erroneous assumptions on cerebral blood flow. Why did not the authors compare their analysis to the “effect site approach” since T Schnider has made a PK/PD analysis of his patients?

As for obese or ICU patients, the authors should confront their simulations to actual data previously published in the literature.

We agree with the reviewer and thus have withdrawn the second paper. The only physiological variable that is now discussed is the effect of obesity. This was an issue that was raised by both reviewer #1 and #3 and we felt it represented an important inference of the PBPK model. The model simulations for the obese subjects are specifically compared with the experimental results of Servin et. al.