Author's response to reviews

Title: Human Physiologically Based Pharmacokinetic Model for Propofol

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Author's response to reviews:

We are, of course, very happy that this manuscript has finally been accepted. Publication will, as Dr. Drover states: "...allow the reader to decide if this contributes to the body of knowledge for propofol and pharmacokinetics in general." Although the reviewing process has been long and difficult, we believe that it has resulted in a significantly improved manuscript, and we wish to thank all the reviewers and editors for the time they spent on this manuscript.

The final version has been only slightly revised from the previous submission. The main change has been to respond to the editors request that we "...particularly and fully acknowledge the limitations of the model with regard to its relevance to real physiological conditions and its applications to other drugs." These changes are described below. The specific changes in the text are indicated by italics.

1) In response to Dr. Upton's comment that: "It is disingenuous to describe the model (e.g. in the abstract) as having only one adjustable parameter, when the fraction of dose sequestered in the lung and it's time constant are also adjusted to achieve fits of the data (3 parameters)" the Abstract has been modified as follows to accurately describe the number of adjustable parameters that were used:

Only one adjustable parameter (the liver clearance) is required to describe the constant infusion phase. In order to fit the bolus injection phase, for 10 or the 24 subjects it was necessary to assume that a fraction of the bolus dose was sequestered and then slowly released from the lungs (characterized by two additional parameters).

In addition, we have added the following sentence to the Introduction:

When a quantitative model (with two additional adjustable parameters) of this sequestration is incorporated into the PBPK model, a single set of PBPK parameters provides a good description of both the bolus and constant infusion phases.

2) The limitations of the evidence for pulmonary sequestration and its applications to humans has now been emphasized in a new paragraph in the Discussion section:

This new evidence supporting the concept of pulmonary sequestration is indirect since it is based just on an analysis of the PBPK model. There clearly is a need for more direct experimental measurements to either confirm or rule out this effect. In addition, the predicted differences in the magnitude of the sequestration between the young and middle-aged subjects is a surprising result and one that requires further documentation.

3) The lack of generality of the PBPK model has now been emphasized by the addition of a new paragraph in the Discussion:

The very high fat solubility of propofol makes it an ideal candidate for a PBPK model. The partition of propofol in tissue fat dominates the tissue/blood partition coefficient, allowing one to estimate the tissue/blood partition simply from knowledge of the tissue fat fraction. For other less fat soluble solutes, the tissue/blood partition cannot be predicted by this a priori approach, and the number of poorly characterized
adjustable PBPK parameters is markedly increased.