Reviewer's report

Title: Human Physiologically Based Pharmacokinetic Model for Propofol

Version: Date: 15 December 2004

Reviewer: Richard Neil Upton

Reviewer's report:

General

The material on propofol kinetics and obesity is a potentially useful addition to the literature, but the author hasn't addressed a number of issues raised in earlier reviews. These deficiencies leave the reader uncertain about the validity of the model.

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

1. The use of age and dose rate dependent lung sequestration of propofol in the model remains controversial and is highly unusual. It therefore requires direct and compelling evidence, which is not yet provided in the paper or available in the literature. The entire model is called into question if this does not occur in man. Most importantly, this sequestration would require substantial differences in kinetics between different propofol formulations (e.g. emulsion and cyclodextrin) in man. This issue should be resolved soon, but no difference was found between these formulations in pigs (Egan, Anesth Analg 2003; 73:97:72–9).

2. 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). There remains no report of the standard errors for the parameter estimates, and correlation between the parameters values. This means that the uniqueness of the model cannot be determined, and that the model building process falls short of accepted modelling practice. Furthermore, no mention of the method used to compare various models (e.g. Akaike Information Criterion) for example to make the decision whether to add or subtract lung sequestration. Again, this fall short of accepted modelling practice.

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

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Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

Unchanged from first review.