Reviewer's report

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

Version: 1 Date: 30 July 2004

Reviewer: Frederique Sylvaine Servin

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This is a very interesting approach of the pharmacokinetics of propofol, through a software already widely used to provide new information on the pharmacokinetics of numerous agents.

I have nevertheless several concerns concerning this work.

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. 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.

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?

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 rebond 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.

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.