Interactive Web Simulation for Propofol and Fospropofol, a New Propofol Prodrug

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Using pharmacokinetic and pharmacodynamic data published in the scientific literature, we have developed interactive on-line simulations to model administration of propofol and fospropofol, a new water-soluble prodrug formulation of propofol. The prodrug formulation of fospropofol leads to a delayed onset to peak concentrations of propofol. A comparison simulation that overlays administration of fospropofol and propofol allows clinicians to understand the differences of administering fospropofol and traditional propofol. The simulations have the added advantage of allowing for differences among patients documented in test studies and the use of different models.

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An acceptable safety profile, speedy onset, and rapid recovery have helped make propofol a popular sedative-hypnotic widely used for producing sedation and inducing general anesthesia.[1,2] A number of disadvantages stem from the formulation of propofol as a lipid emulsion. Chief among these disadvantages are pain on injection,[3,4] risk of infection from decreased bacterial clearance,[5] high lipid intake during long-term administration,[6,7] and dose-related cardiac and respiratory depression.[7] Fospropofol (GPI 15715; Aquavan® Injection, MGI Pharma Inc., Minneapolis, MN) is a water-soluble prodrug of propofol designed to bypass the disadvantages inherent in the lipid formulation of propofol.[8] Although the water-soluble preparation of fospropofol bypasses the disadvantages of lipid formulation, the prodrug preparation leads to a delayed time to peak concentration of propofol. To better understand the distinction between how administration of propofol differs from fospropofol, we have developed propofol and fospropofol simulations (http://vam.anest.ufl.edu/simulations/simulationportfolio.php), including a comparison simulation that overlays administration of fospropofol and propofol (http://vam.anest.ufl.edu/simulations/propofolfospropofolcomparison.php).

Using pharmacokinetic parameters available in the scientific literature,[9–14] we have developed on-line interactive propofol and fospropofol simulations. Of the available published models, the choice of models based on studies conducted by Fechner et al. and Gepts et al. stemmed from the completeness of the pharmacokinetic data provided in their publications and the use of adult subjects. Based on a review of the literature, propofol is modeled using a three-compartment model with peripheral, central, and slow compartments.[12,13] The conversion of the fospropofol prodrug introduces two additional compartments leading to a five-compartment model.[12] The on-line simulation displays drug concentration (*Y*-axis) plotted against time (*X*-axis). The drug concentration range is further demarcated by user-adjustable plasma levels of return of consciousness and loss of consciousness (LOC), default settings from the literature of 1.3 and 2.1 μg/mL, respectively.[8]

Our computer simulations were validated by comparing simulated drug administration to actual values obtained during clinical experimentation. In the Fechner et al. study, groups of three healthy men were administered 10-min infusions of fospropofol with total dosages given being 290, 580, or 1160 mg. The propofol concentration in the central compartment (blood) was obtained before the start of the fospropofol infusions and every 2 min for 30 min after the start of the fospropofol infusions. The propofol concentration in the central compartment was plotted versus time. Using the same total dosages administered through 10-min infusions, we generated similar plots for propofol in the central compartment (Fig. 1).[12]

The simulation models allow users to adjust the following variables: patient weight, infusion rate, infusion duration, initial and second bolus dose, timing of second bolus, and choosing between two models (Fechner et al. or Gepts et al.). Drug concentrations in

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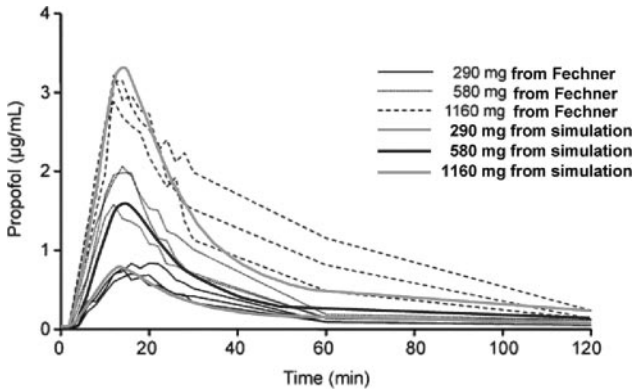

Figure 1. Comparison of the simulation-generated and actual measured propofol concentrations after administration of 290, 580, and 1160 mg fospropofol. Adapted from Fechner et al. *Anesthesiology.* 2003;992:303–13, ©Lippincott Williams & Wilkins.

any of the five compartments can be visualized (Fig. 2). Additionally, there are simulations for modeling the administration of propofol or fospropofol individually, or for simultaneously comparing administrations of the two drugs (Fig. 3).

CASE SIMULATION

Because of the delay in conversion of prodrug to propofol, time to peak propofol concentration after a bolus administration of fospropofol is noticeably longer than after bolus administration of propofol in lipid emulsion (Fig. 4). The elimination of propofol from a bolus administration of fospropofol is also slower than after bolus administration of propofol in lipid emulsion.[10,12] This slower elimination might arguably be advantageous in requiring only a single dose to provide anesthesia for short procedures. However, a slower onset of fospropofol when compared to lipid formulated propofol could also lead novice users to redose fospropofol before the peak effect has occurred. This could lead to excessive second peaks and also cause delayed emergence at the end of short procedures. The slower onset and redistribution into more compartments translates into an attenuated peak for fospropofol compared to propofol. Manipulation of the doses and timing allowed by the simulation can be done to demonstrate these phenomena.

Using the highest-recommended fospropofol dosage of 12.5 mg/kg,[8] a single administration does not reach levels sufficient for LOC until 4 min, compared with LOC after one circulatory time with the highest recommended dosing with propofol of 2.5 mg/kg (Fig. 4).[8]

Onset of sedation with fospropofol is reported to have a median time of 2 min from administration.[8] Administering a half-initial dose after 2 min, as might occur by an anxious clinician wishing to proceed with sedation, results in the profile in Figure 5. Not only is there no appreciable improvement in onset time, but return of levels to LOC threshold takes 20 min. This may lead to prohibitive delays and prolonged periods of LOC during quick procedures, such as colonoscopies, for which fospropofol is intended.[15]

CONCLUSION

We have used existing pharmacokinetic and pharmacodynamic data available in the scientific

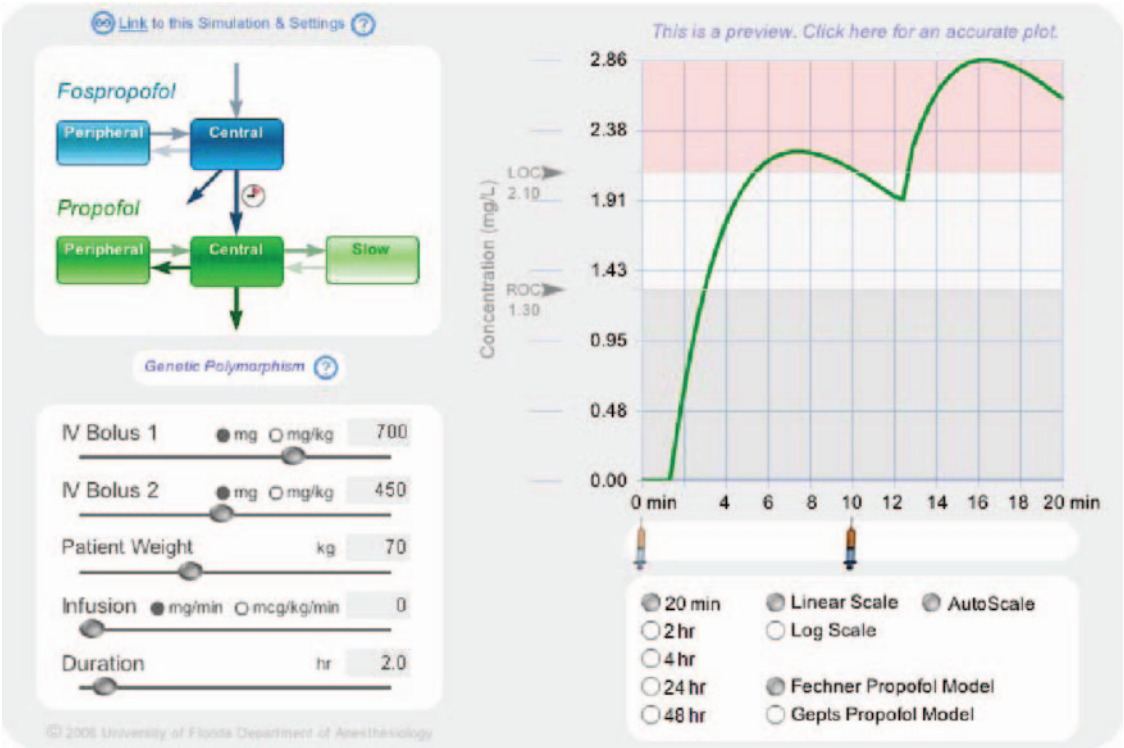

Figure 2. Sample screen shot for simulation of fospropofol administration.

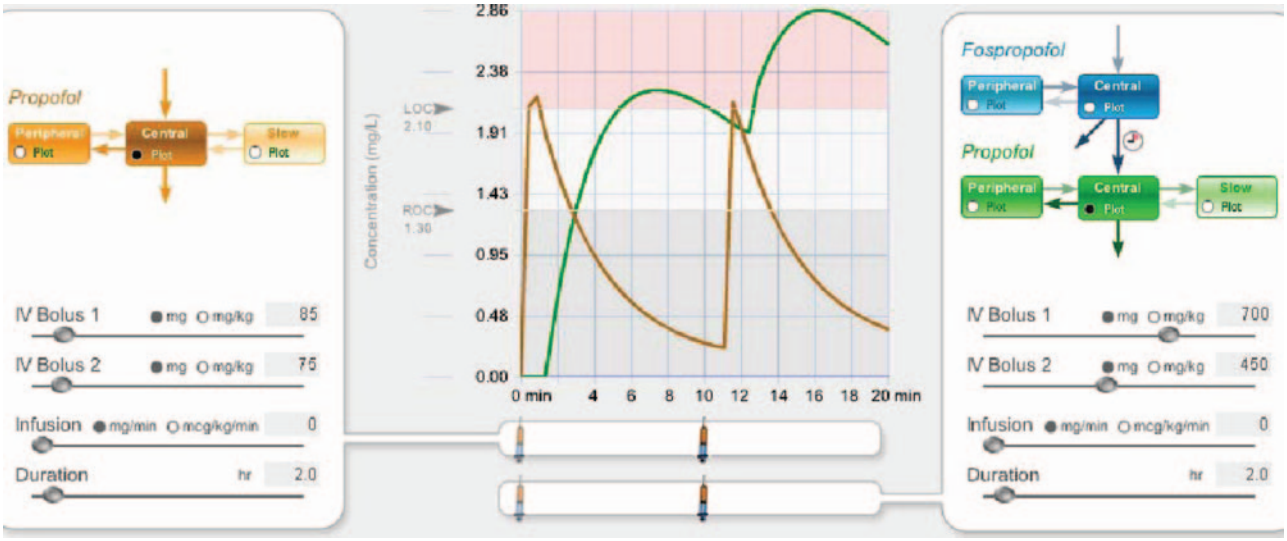

Figure 3. Sample screen shot for simulation comparing propofol and fospropofol administration.

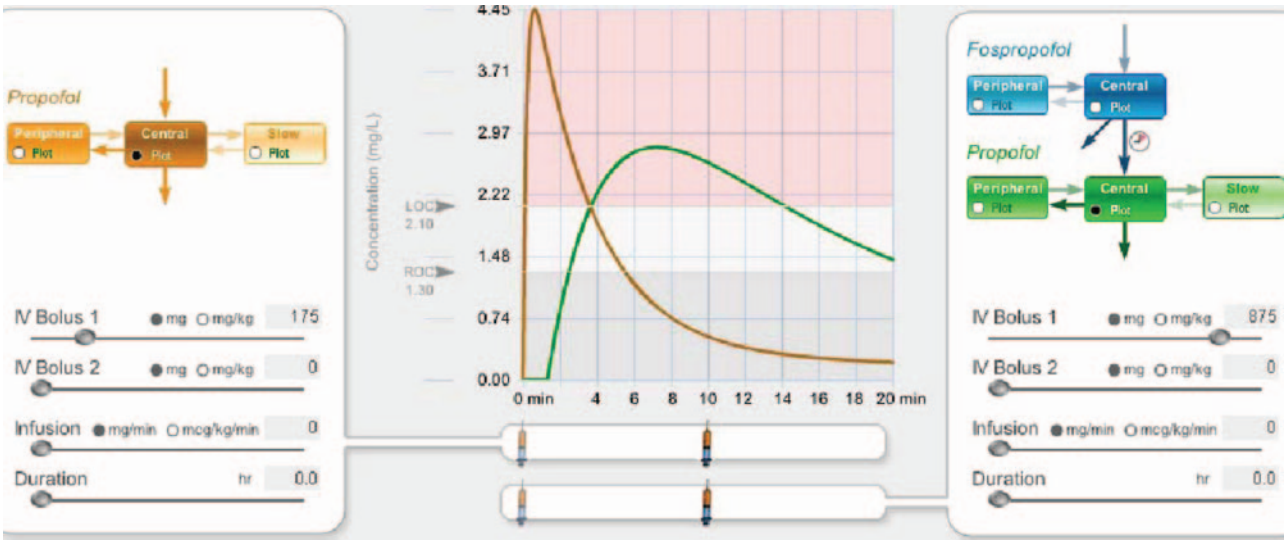

Figure 4. Green line: Plot of propofol concentrations following administration of fospropofol 875 mg (12.5 mg/kg for a 70 kg patient), using the Fechner et al. model. Brown line: Plot of propofol concentrations following administration of propofol 175 mg bolus (2.5 mg/kg for a 70 kg patient), using the Fechner et al. model.

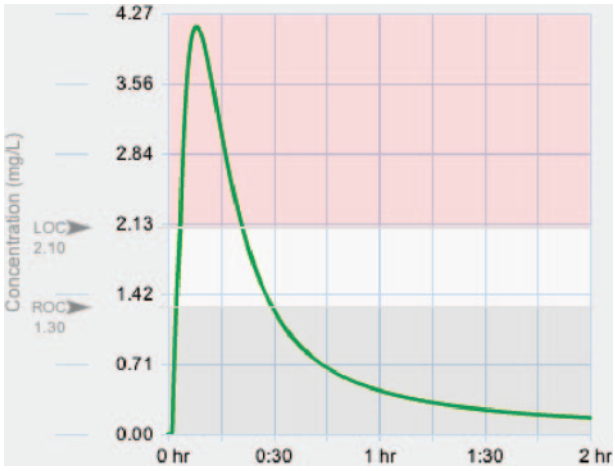

Figure 5. Plot of propofol concentration after administration of fospropofol 875 mg (12.5 mg/kg for a 70 kg patient) followed by 435 mg (6.2 mg/kg for a 70 kg patient) at 2 minutes, using the Fechner et al. model.

literature to develop a user-friendly on-line computer simulation. This simulation helps practitioners familiar with the use of a commonly administered drug, propofol, to familiarize themselves with the administration of a similar new prodrug, fospropofol. The simulation also produces an opportunity to model the spectrum of interpatient and pharmacokinetic model variability by activating the genetic polymorphism and model choice functions using the published models of Fechner et al.[12] and Gepts et al.[13] We believe such interactive models may provide a realistic and real-time method for practitioners to familiarize themselves with dispensing a new drug and experiment with different administration regimes and targets.

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