Parameter Estimation on a Physiologically Based PK/PD Model for Dose-Dependent Intravenous Lipid Emulsion Therapy in Rats

M. McDaniel, K. Flores, B. Akpa
North Carolina State University

Purpose

Intravenous lipid emulsion (ILE) therapy has spurred recovery from cardiac arrest induced by local anesthetic overdose in multiple documented cases. Characterizing the mechanism by which it promotes cardiac recovery is a critical step in establishing ILE therapy as a viable option in overdose cases. Previous research has indicated that, in addition to sequestering toxins away from the heart, lipid emulsions introduce a flow-promoting effect that further enhances cardiac function. The purpose of this study is to estimate physiological parameters associated with lipid response in rats using a compartmental pharmacokinetic/pharmacodynamic (PK/PD) model and to predict the subjects' response to simulated anesthetic overdose.

Methods

The data used for analysis were drawn from a study in which the cardiac outputs of seven rats were monitored for ten minutes following injection of 9 mL/kg of a 20% lipid emulsion. The lipid dosage was administered over a 60 second interval. Six parameters were estimated: Four physiological parameters and two control variables introduced to the model to capture the action of homeostasis. The four physiological parameters were assumed to remain constant on an individual basis and the control variables were allowed to vary temporally. Time variation was accomplished using evenly spaced linear splines. Models with one (i.e. constant), two, five, and nine splines were investigated. Parameter estimation was performed by employing a global search followed by non-linear least squares regression. The efficacy of each model was qualified by Akaike Information Criterion (AIC). A virtual population was constructed to model an average response to an overdose of the anesthetic bupivacaine followed by one of three ILE treatments described in literature.

Results

The model fit with nine splines was determined to provide the best fit for each rat by AIC scoring (See Figure 1 for sample fit). The distribution of each parameter was heavy-tailed in nature, leading to the assumption that the parameters in question were log-normally distributed across the population. The ten thousand realizations necessary to construct the virtual populations were created by sampling from these log-normal parameter sets. The virtual populations (Figure 2) exhibited the ability of ILE therapy to promote cardiac recovery after near fatal decreases in cardiac output brought on by bupivacaine overdose. Furthermore, the speed and shape of the response were consistent with previous experiments in rats.

Conclusion

We have shown that we can model the response of rats to intravenous lipid emulsion therapy via estimation of physiologically relevant parameters. Model fits were improved by allowing for time variation in the control parameters describing the homeostatic response of the subject. Virtual population simulations utilizing the estimated parameters were consistent with in vivo experimentation. Future work will seek to estimate physiological parameters associated with bupivacaine response on an individual level. We are confident that this additional information will help us to accurately assess treatment dosage and response on an individual level.