**Influence of the Method of PK and PD Modeling on the Objective Function and the PD Parameters**

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**Background/Introduction:** There are many methods of modeling pharmacokinetic (PK), pharmacodynamic (PD) and combined pharmacokinetic/pharmacodynamic (PK/PD) relationships. We investigated how the modeling method influences the objective function and the final PD parameters.

**Methods:** After IRB approval, 15 patients were monitored with Bispectral Index (BIS) while receiving propofol at 40 mg/kg/h. Once maximum burst-suppression was observed, propofol infusion was stopped, and the BIS was recorded until return of consciousness. The following PK/PD methods were applied using NONMEM 7.2: Individual PK Parameters (IPP), Population PK Parameters & Data (PPP&D) and Simultaneous (SIM)1. For PD modeling, we used a symmetrical Emax model (SYM), 2 separate ke0s for induction and recovery (switchpoint at end of infusion, [2KI], or time of lowest BIS, [2KL]) and 2 effect-site compartments (2EC).

**Results:** The model with lowest objective function value (OFV) was 2EC for the IPP method. For the combined PK/PD modeling (PPP&D and SIM), PPP&D-2KL had the lowest OFV. The C50s ranged between 1.78 and 5.56 µg/ml. Ke0s (SYM and 2EC) ranged from 0.091 to 0.345 min-1. Ke0i (induction) was consistently higher than ke0r (recovery) in the IPP method (0.309-0.339 vs. 0.0724-0.0740, respectively), but lower in the PPP&D and SIM methods (0.0901-0.240 vs. 0.226-0.488).

The more complex PK/PD-modeling (SIM and, to a lesser extent, PPP&D), caused more model instability, which could only be prevented by reducing the number of inter-individual variability () estimations. With this method 2-compartment PK-models often produced better PD-fits.

**Conclusion:** The method of PK/PD and PD modeling greatly influences fit and PD parameters. It is important to investigate the different methods to find the most appropriate model as the PK method influences the PD and vice versa. The decision over which model is ‘best’ also depends on whether the goal of the model is to focus on the effect (PD) or plasma concentration (PK).

**References:**

1 Zhang L, Beal SL and Sheiner LB. Simultaneous vs. Sequential Analysis for Population

PK/PD Data I: Best-case Performance. J Pharmacokinet Pharmacodyn 2003: 30; 387-404