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 ways to model pharmacodynamics (PD) and combined pharmacokinetics/pharmacodynamics (PKPD). We investigated how the modeling method influences the objective function and the final PD parameters.

Methods:
After IRB approval, 15 patients, monitored with Bispectral Index (BIS), received propofol at 40 mg/kg/h until maximum burst-suppression. The study ended after return of consciousness. Several PKPD methods were tested using NONMEM 7.2: Individual PK Parameters (IPP), Population PK Parameters & Data (PPP&D) and Simultaneous (SIM)[1]. For PD, we tested a symmetrical Emax model (SYM), 2 separate keOs for induction and recovery (switchpoint at end of infusion, [2KI], or 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 PKPD modeling (PPP&D and SIM), PPP&D-2KL had the lowest OFV. The C50s ranged between 1.78-5.56. KeOs (SYM and 2EC) ranged from 0.091-0.345. KeOi (induction) was consistently higher than keOr (recovery) in the IPP method (0.309-0.396 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 PKPD-modeling (SIM and, to a lesser extent, PPP&D), caused more model instability, forcing the need reduce the number of inter-individual variability (η) estimations, and often with 2-compartment PK-models producing better PD-fits.

Conclusion:
This study shows that the method of PKPD 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 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