Comparative Evaluation of Bias And Precision in Compartmental Models of Enterohepatic Circulation

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Objectives: Enterohepatic circulation (EHC) of drugs can be described as a distribution process in which a fraction of conjugated drug is excreted in bile and transported to the gut, undergoes deconjugation by the gut flora, and then get reabsorbed back to the systemic circulation. The presence of EHC results in changes in the pharmacokinetic profile of the drug. The pharmacokinetic evaluation of drugs exhibiting EHC has been variable in the literature and frequently considers EHC as an elimination process rather than distribution. The objective of this analysis was to evaluate pharmacokinetic bias and precision of several compartmental models used to analyze simulated data from a drug undergoing EHC.

Methods: Stochastic simulation and estimation was implemented using NONMEM and PsN. An oral dosing depot with 1-compartment disposition and semi-mechanistic EHC model that included a gallbladder and continuous bile flow was used to simulate 250 datasets of 50 subjects; samples were obtained at times 0.5, 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours. Patients were assumed to have food intake at times 1, 4 and 10 hours that stimulated gallbladder contraction. The percentage of the drug undergoing EHC (PCT) was 40%. Data analytic models included 1-compartment, 2-compartment, and several plausible EHC-based models with and without a gallbladder, continuous bile flow, and inclusion of 0, 1, 2 or 3 meals. Comparisons of OFV, CL, PCT, BSV, and RUV estimates across models were based on bias and precision.

Results: As expected, the simulation model produced the lowest OFV and smallest bias and imprecision. Inclusion of a gallbladder compartment also provided similar results, but ignoring meals in the model to stimulate gallbladder contractions generally increased bias. Not including a continuous bile flow in the model substantially increased bias in PCT. Both 1- and 2-compartment models produced results with more bias.

Conclusion: This study suggests that when modeling a drug undergoing EHC, it may be important to include a gallbladder compartment, continuous bile flow, and feeding times to minimize bias in parameter estimates.