A pharmacokinetic model for drugs undergoing enterohepatic circulation: A sensitivity analysis

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Objectives: Literature modeling strategies of the EHC varies; however, gallbladder-based models provide the best current physiological representation of the process. Regardless, the addition of a gallbladder into the model does not fully depict the physiology of EHC. A more physiological gallbladder-based EHC model is needed. This model should take into account a physiological representation of the bile secretion, gallbladder filling and emptying, duration of gallbladder emptying and irregular mealtimes. With all these considered, the objectives of the current analysis are to propose a gallbladder-based EHC model; to use the model in performing sensitivity analyses to evaluate the effect of the extent of EHC on the pharmacokinetic profile and the non-compartmental analysis (NCA) calculations.

Methods: A gallbladder-based model that describes the EHC process was developed and used to perform determinant simulations assuming various extents of EHC. Next, these simulations were compared to evaluate the effect of the EHC on the pharmacokinetic profiles of orally administered drugs. The influence of the EHC process on the NCA calculations was determined assuming two sampling schemes that differs by the selected sampling times in relation to meal times.

Results: The presence of EHC results in nonlinearity in the system and causes changes in the pharmacokinetic profile. These changes include effects of Cmax, Tmax, and half-life estimates. The comparison of two sampling schemes from a drug undergoing various degrees of EHC demonstrated a major influence of the selected sampling times on the NCA estimations. Bias in the NCA calculations was dependent on the sampling times.

Conclusion: Caution should be taken when designing clinical studies for drugs that undergo EHC. The timing of meals may be an important factor to consider when designing pharmacokinetic studies and defining sampling times. The duration of sampling needs to be extended over a longer duration than what is traditionally done with other drugs. Future studies that attempt to identify best sampling strategies in the presence of EHC are needed.