Development of a Physiologically Based Pharmacokinetic Model to Predict the Exposure of Itopride in Flavin-Containing Monooxygenase 3 Extensive and Poor Metabolisers

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Objectives: Itopride was approved for the symptomatic treatment of various gastrointestinal disorders in Asian countries and is mainly metabolized by Flavin-Containing Monooxygenase 3 (FMO3). The objective of this study was to develop a physiologically based pharmacokinetic (PBPK) model to capture itopride PK in FMO3 extensive metabolisers (EM) and poor metabolisers (PM).

Methods: Simcyp simulator version 14 release 1 (Certara, Sheffield, UK) was used to conduct all simulations. The Asian population library files within the modeling platform were further developed by incorporating FMO3 enzyme abundance/activity and genotype frequencies which were derived from in vitro human liver microsomes data and clinical pharmacogenetic studies of multiple drugs metabolized by FMO3. A full body distribution model was used to describe tissue-plasma partitioning for itopride with partition coefficients and Vss predicted by the method of Rodgers et al. A first order oral absorption model was applied, using an optimized absorption constant value of 4 /h and an absorption lag time of 0.4 h to recover the clinically observed Tmax. The kinetics of itopride N-oxygenation by FMO3 were obtained from in vitro pooled human liver microsomes studies and verified using clinical observed data. The model was first verified with multiple itopride clinical studies conducted in Japanese and Korean subjects following administration of 150 mg single dose or 50 mg TID itopride, then was applied to predict itopride exposure in Chinese FMO3 EM and PM subjects.

Results: The meta-analysis of relative enzyme activities suggested that FMO3 activity in PM is 47% lower than EM. In a combined Asian population, EMs account for about 5% of the total population. The predicted plasma concentration-time profiles of itopride in Chinese FMO3 EMs and PMs were compared with observation (Figure 1). The PBPK predicted AUC of itopride in Chinese FMO3 PM is 1.6 fold higher than FMO3 EM, which is slightly lower than clinical observation (2.2 fold). The difference is likely caused by the small sample sized in the clinic trial (6 subjects in each group).

Conclusions: The system components describing FMO3 phenotype frequency and relative activity were derived in Asian populations and applied to predict the pharmacokinetics of Itopride. The developed itopride PBPK model could reasonably capture the drug exposure of FMO3 EMs and PMs in a Chinese population.

Figure 1. Mean simulated (solid line) and observed (data points) concentration of itopride after oral administration of a single 50 mg dose to healthy male Chinese FMO3 EMs (A) and PMs (B). The grey lines represent individual trials (20 trials, 6 subjects in each trial) and the solid black line is the mean of the population (n=120).

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