Mechanistic Absorption and Physiologically Based Pharmacokinetic Modeling of Itraconazole and Its Application for Drug-Drug Interaction with Midazolam in Adult Populations

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**Purpose**

Itraconazole (ITZ) is a BCS Class II triazole antifungal (Sporanox; Janssen Pharmaceutica, Titusville, NJ). It is a substrate and potent inhibitor of CYP3A4. The primary metabolite, hydroxy-itraconazole (OH-ITZ) and the two other downstream metabolites, keto-itraconazole (keto-ITZ) and N-desalkyl-itraconazole (ND-ITZ), are also substrates and inhibitors of CYP3A4. The purpose of this study was to develop a PBPK model for ITZ and its metabolites which accounts for all the relevant mechanisms (dissolution, precipitation, absorption, distribution, metabolism, and auto-inhibition) after i.v. and p.o. ITZ administration. This model was validated by predicting effect of ITZ administration on midazolam (MID) pharmacokinetics (PK).

**Methods**

The PBPKPlus™ module in GastroPlus™ (Simulations Plus, Inc.) was used to model the PK of itraconazole and its three metabolites. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, precipitation, and absorption of ITZ after p.o. administration. Human physiologies were generated by the program’s internal Population Estimates for Age-Related (PEAR™) Physiology™ module. Tissue/plasma partition coefficients for all compounds were calculated using the Lukacova algorithm based on tissue composition and in vitro and in silico physicochemical properties. Biopharmaceutical parameters for both ITZ and its metabolites were either obtained from literature or predicted by ADMET Predictor™ 6.5 (Simulations Plus, Inc.). The series of metabolic reactions from ITZ to hydroxy-ITZ to keto-ITZ to ND-ITZ (all catalyzed by the CYP 3A4 enzyme) was modelled by Michaelis-Menten kinetics with in vitro enzyme kinetic parameters along with the GastroPlus built-in expression levels of CYP3A4 in gut and liver. The default dissolution model was used for both solution and capsule dosage forms. Particle size for the capsule dosage form was adjusted to 3μM to account for formulation effects. The program’s mechanistic nucleation model was used to account for possible precipitation as ITZ solubility changed in different intestinal regions. The permeability of ITZ was predicted using MembranePlus™ 1.0 (Simulations Plus, Inc.). The DDI module in GastroPlus was then used to predict the effect of ITZ on MID PK for variety of study designs (varying ITZ and MID doses and administration times).

**Results**

Itraconazole is highly insoluble in water and is subject to precipitation. Clinical studies showed significant food effect on ITZ bioavailability; hence the DDI effect may be different in fasted and fed state. The mechanistic model showed significant precipitation of the solution dose under fed conditions (with 200mg solution dose, 90% of the drug precipitated upon entry into the small intestine). The model explained the mean plasma concentrations for ITZ and its metabolites well for different doses and formulations as well as predicting the effect on MID PK for variety of study designs. In agreement with the experimental reports in literature, the model predicted that about 45% of the total DDI effect is caused by the metabolites, with ND-ITZ being main contributor among all the metabolites.

**Conclusion**

The work described the use the MAM/PBPK approach for drug development and demonstrates the ability to predict DDI interaction with other compounds. MAM/PBPK approach enables incorporation of all the relevant processes in the drug absorption, distribution, metabolism and elimination and helps with prediction of PK for different dosage forms and study designs. The inclusion of all the major downstream metabolites of ITZ was important for accurate prediction of DDI effect.