W5237

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

**Ke X. Szeto, Viera Lukacova, John DiBella, Walter S. Woltosz, and Michael B. Bolger**

Simulations Plus, Inc., 42505 10th Street West, Lancaster, CA 93534, USA

## Introduction

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 was to develop a mechanistic absorption model (MAM)/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 ITZ and the 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 the compounds were calculated using the Lukacova algorithm based on tissue composition and *in vitro* and *in silico* physicochemical properties. The biopharmaceutical parameters for both ITZ and its metabolites were either obtained from literature or predicted by ADMET Predictor™ 6.5 (Simulations Plus, Inc.). The metabolism series from ITZ to OH-ITZ to keto-ITZ to ND-ITZ (all mediated by the CYP3A4 enzyme) was modelled by Michaelis-Menten kinetics with *in vitro* enzyme kinetic parameters and 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 3 µm to account for the formulation effect. The program's mechanistic nucleation and growth (MNG) model was used to account for possible precipitation as ITZ solubility changes in different intestinal regions. The permeability of ITZ was predicted in MembranePlus™ 1.0 (Simulations Plus, Inc). The DDI module in GastroPlus was used to predict the effect of ITZ on MID PK for a variety of study designs (varying ITZ and MID doses and administration times).

**Table 1. Ki and Km values[4].**

| | Ki,u (nM) | Km,u (nM) |
|---|---|---|
| **ITZ** | 1.3 | 3.9 |
| **OH-ITZ** | 14.4 | 27 |
| **Keto-ITZ** | 1.4* | 1.4 |
| **ND-ITZ** | 0.38# | 0.38 |

*Ki,u is the same as Km,u

#Km,u and Ki,u were calculated from IC50,u based on the incubated MDZ concentration 1 uM

**The results of selected doses are shown below:**

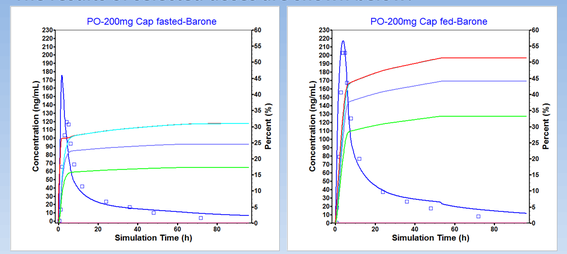


**Figure 1:** Mean simulated (line) and observed (points) pharmacokinetics profiles for ITZ after capsule administration of 200 mg ITZ to a 23-year-old male of 70.9 Kg under fasted (left) and fed (right) condition. Blue colored lines and data points represent plasma concentration (y-axis on the left). The remaining lines represent cumulative amount of ITZ dissolved, absorbed, entering portal vein, entering systemic circulation, and total precipitated, all shown as percent of the administered dose (y-axis on the right)

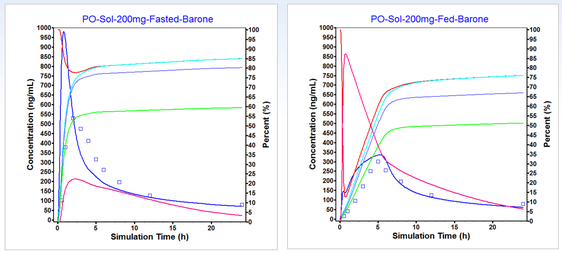


**Figure 2:** Mean simulated (line) and observed (points) pharmacokinetics profiles for ITZ after capsule administration of 200 mg ITZ to a 23-year-old male of 70.9 Kg under fasted (left) and fed (right) condition. The color-coded lines follow the same definition as in Figure 1.

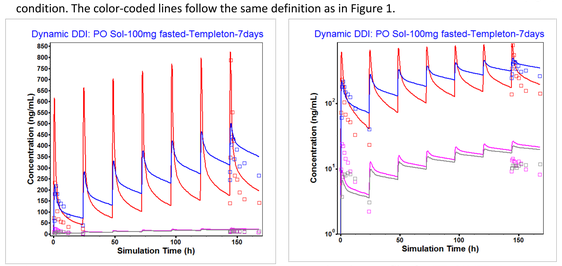


**Figure 3:** Simulated (lines) and observed plasma concentration time profiles for ITZ, OH-ITZ, Keto-ITZ, and ND-ITZ after ITZ solution administration once-a-day for 7 days under fasted condition. **Left:** Normal scale. **Right:** Log scale.

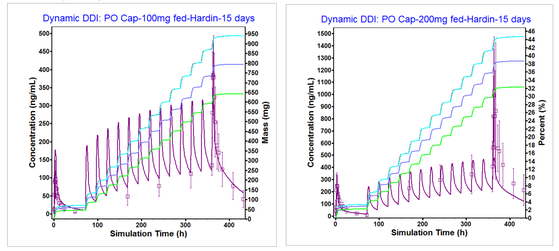


**Figure 4:** Simulated (purple lines) and observed plasma concentration time profiles (purple squares) for ITZ after ITZ capsule administration once-a-day for 15 days under fed condition. **Left:**100 mg once a day. **Right:** 200 mg once a day. The remaining lines represent cumulative amount of ITZ dissolved, absorbed, entering portal vein and entering systemic circulation, all shown as percent of the administered dose (y-axis on the right).

## Results

**Part I: Overall performance on ITZ-MDZ drug-drug interaction prediction.**

Table 2 summarizes the literature data on drug-drug interaction between ITZ and MID [5-9]. The first three studies used solution dosage forms while the rest used capsule dosage forms of ITZ. The demographic information and study protocol are also provided in the same table. On the day of MID administration, we assumed the subjects were in fed state for 3 hours after lunch and then switched to fasted state. Since both MID and ITZ are sensitive to prandial states, it is important to specify the physiological changes according to the meal schedule in the DDI simulations.

**Table 2. DDI study design details.**

| Trial No. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| ITZ | 50 mg SD | 200 mg SD | 400 mg SD | 200 mg SD |
| Midazolam | 2 mg taken 4 hours after the inhibitor dose | 2 mg taken 4 hours after the inhibitor dose | 2 mg taken 4 hours after the inhibitor dose | 7.5 mg po taken 2 hours after the inhibitor dose on day 1 |
| Demographics of HVs (M:F) | n=6 (5:1); age 22-42 yrs | n=6 (5:1); age 22-42 yrs | n=6 (5:1); age 22-42 yrs | n=12 (7:5); age 19-25 yrs; weight 57-95 kg |
| Study Protocol | Didn't mention, assumed Fasted | Didn't mention, assumed Fasted | Didn't mention, assumed Fasted | Volunteers fasted for 3 hours. |
| Reference | Templeton et al. 2010 | Templeton et al. 2010 | Templeton et al. 2010 | Olkkola et al. 1996 |

| Trial No. | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|
| ITZ | 200 mg QD for 6 days | 100 mg QD for 4 days | 200 mg QD for 6 days | 200 mg QD for 4 days | 200 mg QD for 4 days |
| Midazolam | 0.05 mg/kg IV over 2 min, 2 hours after the inhibitor dose on day 4 | 7.5 mg po taken 2 hours after the inhibitor dose on day 4 | 7.5 mg po taken 2 hours after the inhibitor dose on day 6 | 15 mg taken 2 hours after the inhibitor dose on day 4 | 7.5 mg po taken 1 hour after the inhibitor dose on day 4 |
| Demographics (M:F) | n=12 (7:5); age 19-25 yrs; weight 57-95 kg | n=12 (4:8); age 19-30 yrs; weight 54-98 kg | n=12 (7:5); age 19-25 yrs; weight 57-95 kg | n=9 (4:5); age 22-34 yrs; weight 55-78 kg | n=9 (2:7); age 19-26 yrs; weight 52-85 kg |
| Study Protocol | Volunteers fasted for 3 hours. | Volunteers fasted for 3 hours. | Volunteers fasted for 3 hours. | Volunteers fasted for 2 hours. | Volunteers fasted for 3 hours. |
| Reference | Olkkola et al. 1996 | Ahonen et al. 1995 | Olkkola et al. 1996 | Backman et al. 1998 | Olkkola et al. 1994 |

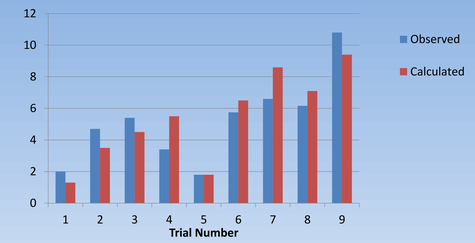


**Figure 5:** Predicted (blue) and observed (green) fold changes in AUC ratios for midazolam under ITZ inhibition effect. Note that study 9 has been corrected for gender effect on CYP3A4 expression level.

**Part II: DDI Contribution from ITZ and its metabolites**

Lastly, in this section, we discuss the individual contribution of ITZ and its metabolites to the overall DDI effect. Here we simulated the inhibition effect of 100mg ITZ on oral MID tablets (7.5 mg) 4 days after the treatment. Table 3 summarizes the predicted AUC ratios under different model settings: 4 competitive substrates (ITZ, hydroxyl-ITZ, keto-ITZ, ND-ITZ), 3 substrates (ITZ, hydroxyl-ITZ, keto-ITZ), 2 substrates (ITZ, hydroxyl-ITZ) and 1 substrate (ITZ). The metabolites contributed about 45% of the total change of AUC and ND-ITZ was the main contributor among all the metabolites. This result is consistent with data published in literature suggesting that ND-ITZ was the most potent inhibitor among ITZ and its metabolites [10], and that 50% of inhibition is associated with the metabolites of ITZ [5].

**Table 3. DDI contribution from ITZ and its metabolites.**

| ITZ model (number of subs) | 4 | 3 | 2 | 1 | Obs Values[6] |
|---|---|---|---|---|---|
| AUC_competitive (ng-h/mL) | 433.10 | 303.60 | 269.30 | 244.50 | 586 |
| AUC_baseline (ng-h/mL) | 66.10 | 66.10 | 66.10 | 66.10 | 102 |
| Ratio of AUC's | 6.55 | 4.59 | 4.07 | 3.70 | 5.75 |

## CONCLUSIONS

The work demonstrates the use of the GastroPlus MAM/PBPK approach to predict DDI interactions involving not only perpetrator, but its multiple metabolites (and metabolites of metabolites). The MAM/PBPK approach incorporates all relevant processes in drug absorption, distribution, metabolism, and elimination and helps with prediction of PK for different dosage forms and study designs. Including all the major downstream metabolites of ITZ was important for accurate prediction of the DDI effect. The overall results presented in Figure 5 show that the model predicts accurately across different studies for both solution and capsule doses using the MNG precipitation model. To conclude, we have shown that the GastroPlus MAM/PBPK approach, integrating relevant physicochemical processes and physiological details, is a highly valuable and reliable predictive utility.

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