Simulations of the dynamic itraconazole and midazolam interaction using individual coupled whole-body physiologically-based pharmacokinetic models

Andrea N. Edginton[1], Michaela Vossen[1], Michael Sevestre[2], Christoph Niederalt[1], In-Jin Jang[3], Stefan Willmann[1]

1) Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany

2) Computational Solutions, Bayer Technology Services GmbH, Leverkusen, Germany

3) Dept of Pharmacology and Clinical Pharmacology, Seoul National University College of Medicine and Hospital, Seoul, South Korea

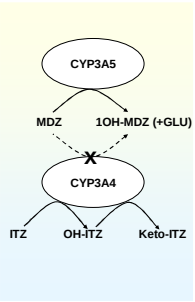
INTRODUCTION

- Physiologically-based pharmacokinetic (PBPK) modeling is a tool for the simulation of concentration-time profiles based on physiology (body and organ weights, blood flows, tissue composition etc.).
- Coupling PBPK models provides the opportunity to dynamically predict the interaction potential of two simultaneously administered compounds.
- **Objective:** To predict the effect of itraconazole (ITZ) CYP3A4 inhibition on midazolam (MDZ) pharmacokinetics using individualized PBPK modeling. Herein, we use MDZ, 1OH-MDZ and 1OH-MDZ-GLU plasma concentration time data from 19 CYP3A5 genotyped (*1/*1, *1/*3, *3/*3) adults, who received MDZ intravenously in basal and CYP3A-inhibited metabolic states caused by ITZ co-administration [1].

METHODS

Defining the MDZ, 1OH-MDZ and 1OH-MDZ-GLU link

- For each individual (n = 19), three PBPK models (MDZ, 1OH-MDZ and 1OH-MDZ-GLU) were generated and dynamically linked such that the source functions of the two metabolites were the hepatic metabolism of MDZ and 1OH-MDZ, respectively.
- Microconstants (**Eq. 1**) in the liver intracellular space defined the link functions and were optimized for each individual using an average CYP3A concentration (E_o) of 2.8 nmol per g liver. Resulting individualized K_m and V_{max} values in different CYP3A5 genotype groups were compared.



$$E_0 + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E_0 + P \qquad \text{(Eq 1)}$$

Modeling CYP3A inhibition by Itraconazole

- Three sources of information were required to generate a model for ITZ and OH-ITZ. These were:
  - PBPK model for the oral administration of ITZ (intracellular unbound concentrations)
  - Time-dependent ratios between ITZ and OH-ITZ concentrations [2] were used to calculate OH-ITZ concentrations from ITZ concentrations
  - In vitro measure of CYP3A4 inhibition by ITZ and OH-ITZ [3]

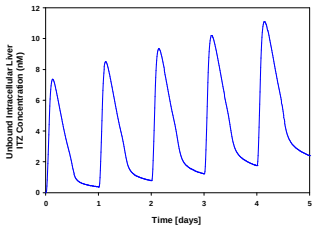


Figure 1. Simulated unbound intracellular liver concentrations following a multiple 200 mg ITZ oral administration.

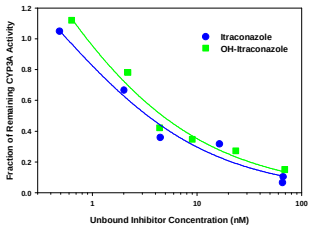


Figure 2. Fraction of remaining CYP3A activity (as derived using MDZ as a substrate) in relation to the unbound inhibitor concentration, in this case ITZ and OH-ITZ [3].

Coupling and Evaluating MDZ and ITZ Models

- For each individual [1], the previously built MDZ model was dynamically coupled to the ITZ/OH-ITZ model where the presence of ITZ reduced CYP3A activity.
- MDZ plasma concentrations with and without ITZ CYP3A inhibition were plotted within CYP3A5 genotype groups and compared to experimental data [1].

RESULTS

Determination of MDZ microconstants

- Resulting K_m and V_{max} values for CYP3A are presented in **Fig. 3** and are not correlated to CYP3A5 genotype
- The mean K_m value (2.8 µM) was similar to the experimentally derived *in vitro* value of 3.9 µM [4].
- Inter-individual V_{max} variability was approximately 5-fold. This variability theoretically accounts for different CYP3A abundances in the individuals from the Yu et al study [1].
- Optimized MDZ and MDZ metabolite curves (**Fig. 4**, blue lines) well fit the experimental data.

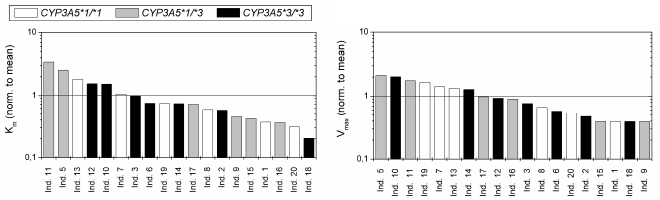


Figure 3. Rank order plots of the resulting K_m and V_{max} values, normalized to the mean, for the hydroxylation of MDZ to 1OH-MDZ mediated by CYP3A.

Modeling CYP3A inhibition by ITZ

- In the inhibited state (**Fig 4**, red lines) the clearance of MDZ decreases inline with experimental data
- MDZ curve shape differs from that of the study data due to potential differences in ITZ PK curve shape in this group.
- In the inhibited state, metabolite concentrations are initially lower and the kinetic differs (despite having the same 1OH and 1OH-GLU clearance as in the basal state).
- There is a greater lack-of-fit for MDZ in CYP3A5 *1/*1 than in CYP3A5 *3/*3. This is due to the greater proportion of CYP3A being 3A5 in *1/*1 individuals whereas ITZ only inhibits 3A4.

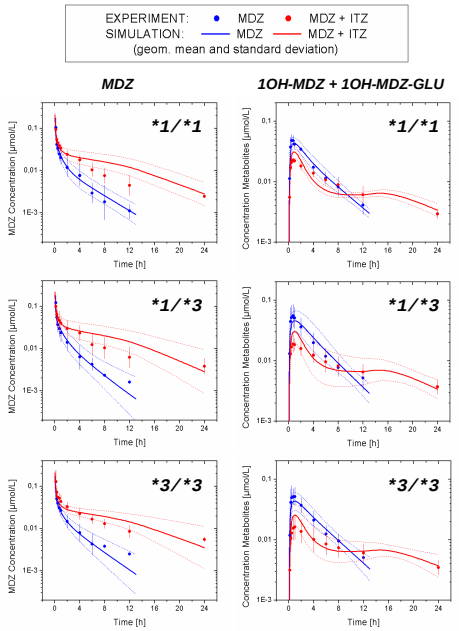


Figure 4. MDZ and the sum of 1OH-MDZ + 1OH-MDZ-GLU concentrations vs time for 19 individuals administered 1 mg MDZ as an intravenous dose. Blue lines represent the optimized curves for each genotype group and red lines represent the predicted curves following oral administration of ITZ for five days with MDZ given on the fifth day.

CONCLUSIONS

- **PBPK modeling describes the plasma kinetics of MDZ, ITZ and their major metabolites.**
- **By dynamically coupling the MDZ and ITZ PBPK models, the relative changes in MDZ, 1OH-MDZ and 1OH-MDZ-GLU pharmacokinetics caused by CYP3A inhibition can be predicted.**
- **Dynamically coupled PBPK models are well suited to predict drug-drug interactions.**

References: [1] Yu et al. *Clin. Pharmacol. Ther.* 76:104 - 12 (2004). [2] Barone et al. *Antimicrob. Agents Chemother.* 37:778 - 84. (1993). [3] Isoherranen et al. *Drug Meta. Dis.* 32:1121 - 31 (2004). [4] Pataki et al. *Drug Meta. Dis.* 31:938 - 44 (2003).

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