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

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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 used 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) of 2.8 nmol per g liver. Resulting individualized Km and Vmax values in different CYP3A5 genotype groups were compared.

\[
E_0 + S \xrightarrow{k_{i1}} ES \xrightarrow{k_2} E_0 + P \quad \text{(Eq 1)}
\]

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]

RESULTS

Determination of MDZ microconstants
- Resulting Km and Vmax values for CYP3A are presented in Fig. 3 and are not correlated to CYP3A5 genotype
- The mean Km value (2.8 μM) was similar to the experimentally derived in vitro value of 3.9 μM [4].
- Inter-individual Vmax 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.

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.