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Prediction of drug-drug interaction (DDI) between cilostazol and substrates or inhibitors of CYP 2C19 and 3A4

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Aim

The aim of this study was to validate the utility of physiologically based pharmacokinetic (PBPK) models for prediction of DDI between cilostazol, ketoconazole, omeprazole and quinidine.

Methods

The absorption and pharmacokinetics (PK) of all drugs were simulated using GastroPlus™ 7.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the absorption, while PK was simulated with its PBPKPlus™ module. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients (Kps) were calculated using a modified Rodgers algorithm based on tissue composition and *in vitro* and *in silico* physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA). Metabolic clearances of all drugs in gut and liver were based on built-in *in vivo* values for the distribution of 3A4 in gut and the average expressions of each involved enzyme in liver. Enzyme kinetic constants were either *in vitro* values from literature, or fitted against *in vivo* plasma-concentration time (Cp-time) profiles. Absorption/PBPK models for all compounds were validated by comparison of simulated and experimental Cp-time profiles for various doses after *i.v.* and *p.o.* administration (Figures 1-4). Dynamic simulations by the GastroPlus 7.0 DDI Module predicted the interactions of cilostazol with individual compounds.

Omeprazole is unstable at low pH and undergoes fast degradation in stomach in fasted state. Administration of buffered solution or enteric coated pellets is generally used to overcome this problem. Polymorphism in 2C19 affects the contributions of individual enzymes to the metabolism of omeprazole as well as overall omeprazole exposure. Both omeprazole dosage forms as well as effects of 2C19 polymorphism were included in predictions of omeprazole-cilostazol DDI. Effects of food on the magnitude of possible drug-drug interaction were investigated for all compounds. The importance of CYP 3A4 and 3A5 contributions to cilostazol metabolism were also explored by assuming that 1) the interacting compounds do not affect 3A5, 2) the interacting compounds affect both 3A4 and 3A5.

Results

The dynamic simulations predicted ~1.4-2 fold increase in cilostazol AUC upon coadministration of 100 mg of cilostazol with 400 mg of ketoconazole. Due to the low contribution of CYP 2C19 to cilostazol metabolism and weak activity of CYP 3A4 in metabolizing omeprazole, the prediction did not show a significant effect of omeprazole on cilostazol PK. Quinidine is metabolized by CYP 3A4, one of the major metabolizing enzymes of cilostazol, giving a potential for competitive inhibition of this enzyme. However, the prediction again did not show significant DDI upon coadministration of 100mg of cilostazol with 200mg of quinidine (only a predicted 1.2-fold increase in cilostazol AUC). All predictions are in close agreement with reported clinical outcomes where ketoconazole caused 2.2-fold increase in cilostazol AUC, while quinidine and omeprazole coadministration did not affect metabolism of cilostazol.

Table 1. *Summary of predicted and observed DDI after administration of cilostazol with omeprazole, quinidine and ketoconazole. Predicted ranges show the magnitude of interaction assuming that the interacting compound affects only 3A4 and both 3A4 and 3A5. All predictions were done for fasted as well as fed state. No interaction was predicted for omeprazole and quinidine, weak-to-moderate interaction was predicted for ketoconazole. Neither dosage form nor 2C19 polymorphism affected the omeprazole-cilostazol DDI.*

Interacting Compound	Observed AUC ratio	Predicted AUC ratio
Omeprazole	1.27	fasted: **1** (all scenarios) fed: **1** (all scenarios)
Quinidine	0.9	fasted: **1.1**(3A4) - **1.2**(3A4/5) fed: **1.1**(3A4) - **1.2**(3A4/5)
Ketoconazole	2.2	fasted: **1.35**(3A4) - **1.72**(3A4/5) fed: **1.49**(3A4) - **2.05**(3A4/5)

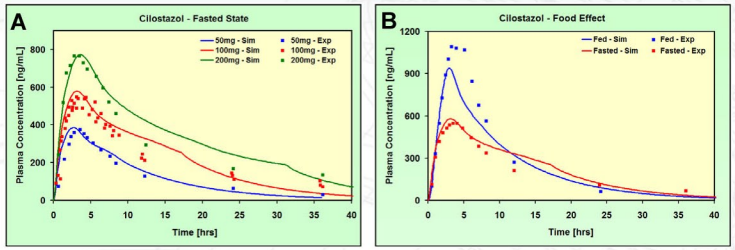

Figure 1. *Simulated (solid lines) and observed (points) Cp-time profiles for: A) different doses of cilostazol IR tablets administered in fasted state, B) 100mg dose of cilostazol IR tablet administered in fasted and fed state*

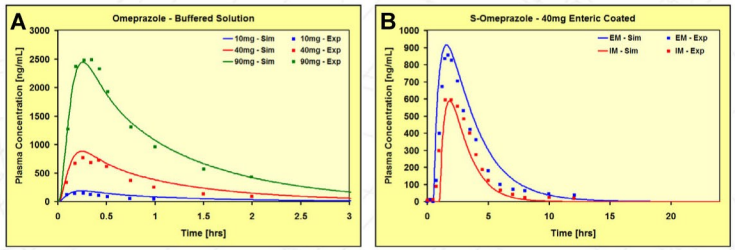

Figure 2. *Simulated (solid lines) and observed (points) Cp-time profiles for: A) different doses of omeprazole buffered solution in a population of extensive metabolizers, B) 100mg dose of S-omeprazole enteric coated formulation in populations of extensive and intermediate metabolizers. All profiles represent fasted conditions.*

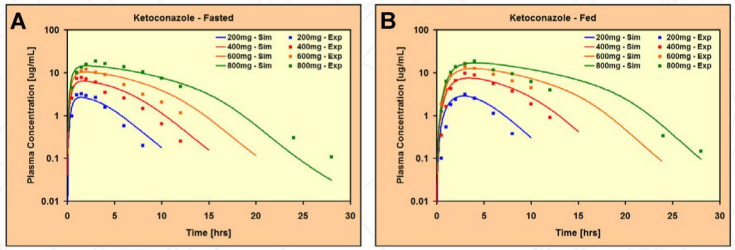

Figure 3. *Simulated (solid lines) and observed (points) Cp-time profiles for different doses of ketoconazole IR tablets administered in fasted state (A) and fed state (B).*

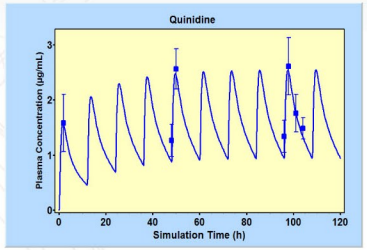

Figure 4. *Simulated (solid lines) and observed (points) Cp-time profiles after repeated administration (every 12 hours) of 500mg of quinidine bisulfate in fasted state*

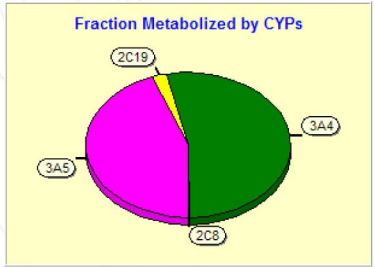

Figure 5. *Metabolic profile for cilostazol. Based on in vitro measurement with recombinant enzymes (assuming the same activity of each enzyme in rCYP system as in liver microsomes). CYPs 3A4 and 3A5 are mainly responsible for metabolism of cilostazol.*

Conclusions

Dynamic simulations utilizing PBPK models with detailed descriptions of each drug's metabolism resulted in accurate predictions of interaction potentials of cilostazol with substrates and inhibitors of its major metabolizing enzymes. Simulations allowed quick exploration of the effects of different formulations, polymorphic enzyme expression and food on the DDI.

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