Omeprazole: Physiologically Based Pharmacokinetic (PBPK) Modeling and Prediction of Drug-Drug Interactions (DDI)

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Purpose: To optimize a PBPK model of omeprazole for prediction of DDIs with respect to polymorphic expression of CYP enzymes.

Methods: Omeprazole absorption and pharmacokinetics were simulated using GastroPlus™ 6.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental and Transit (ACAT) model described the absorption of the drug, while pharmacokinetics was simulated with its PBPKPlus™ module. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients 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). The metabolic clearance of omeprazole in gut and liver was based on *in vitro* enzyme kinetic constants for CYP3A4, 2C9 and 2C19 combined with built-in *in vitro* values for the distribution of 3A4 in gut and the average expressions of all three enzymes in liver. A test version of the upcoming DDI Module in GastroPlus was used to predict the DDIs with different drugs.

Results: Simulated plasma concentration-time profiles for *i.v.* and *p.o.* doses over the range of 10-90 mg closely matched *in vivo* data reported in literature. The simulated gut and liver concentrations of omeprazole, which were used as estimates of effective inhibitor concentrations, accurately predicted DDIs where omeprazole had the role of the "perpetrator" drug. The simulated *in vivo* metabolic profile was used for estimates of contributions of individual enzymes to omeprazole's metabolism for predictions of DDIs where omeprazole was the "victim" drug.

Conclusions: Omeprazole is eliminated mainly by metabolism and is an inhibitor of several CYPs. Depending on the co-administered drug, it can act as "perpetrator" as well as "victim" drug. The GastroPlus PBPKPlus module, combined with a detailed description of omeprazole's metabolism, provided a framework for prediction of DDIs in both cases and also allowed for stochastic variability of the DDI to be introduced in populations with polymorphic expression of the CYPs.

References:

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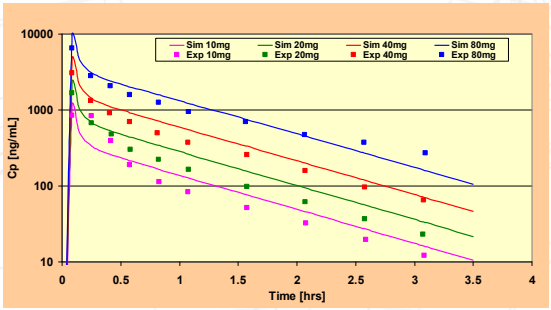
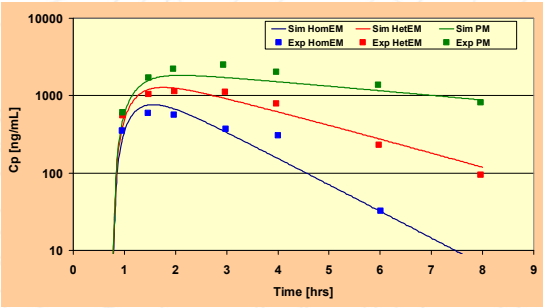
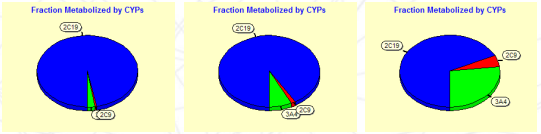


Plasma concentration vs. time profiles after IV administration of 10 – 80 mg of omeprazole

In vitro enzyme kinetic constants for CYP3A4, 2C9 and 2C19 resulted in a good match between simulated and experimental Cp-time profiles for homozygous extensive metabolizers (HomEM). To account for the modified binding sites in heterozygous extensive (HetEM) and poor metabolizers (PM), the 2C19 K_m for each group was fitted against corresponding Cp-time profile.



Plasma concentration vs. time profiles after PO administration of 40 mg of omeprazole in homozygous (Hom) and heterozygous (Het) extensive metabolizers (EM), and poor metabolizers (PM)



Metabolic profiles of omeprazole in homozygous (Hom) and heterozygous (Het) extensive metabolizers (EM) and poor metabolizers (PM) resulting from 2C19 Km fitting against corresponding Cp-time profiles

Predicted and experimental DDI of omeprazole with inhibitors fluconazole and fluvoxamine and substrates cilostazol and diazepam

Inhibitor	Substrate	AUC(inh)/AUC predicted	AUC(inh)/AUC observed
fluconazole	omeprazole	7.9	5.65
fluvoxamine (EM Hom)	omeprazole	4.64	4.86
fluvoxamine (EM Het)	omeprazole	2.74	2.08
fluvoxamine (PM)	omeprazole	1.35	1.23
omeprazole[#]	cilostazol	1.1	1.26
omeprazole[$]	diazepam (IV)	1.09	1.26

- DDI mainly due to inhibition of intestinal 3A4

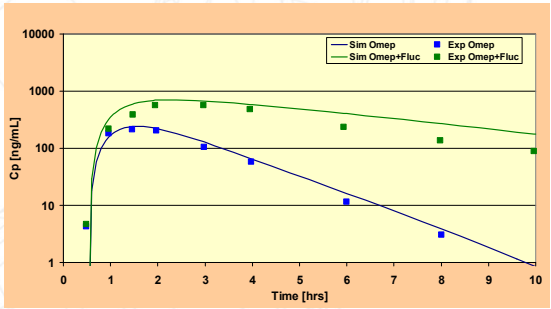
$ - DDI due to inhibition of liver 2C19

The steady-state DDI predictions for omeprazole with substrates cilostazol and diazepam were obtained using a test version of the upcoming DDI Module in GastroPlus.

A more detailed analysis was performed for the interaction of omeprazole with the 2C19 inhibitors fluconazole and fluvoxamine. These two compounds are competitive inhibitors of 2C19, but are not metabolized by the same enzyme, so their pharmacokinetics is not affected by the coadministration with omeprazole. Simulations using previously fitted absorption/PBPK models for these two compounds also showed relatively small changes in unbound liver concentrations over the time period of interest. Therefore, their effect on omeprazole clearance could be directly incorporated in the form of a K_m adjustment. The apparent omeprazole K_m for 2C19 in the presence of these two inhibitors was calculated as:

$$Km_{app} = Km \times \left(1 + \frac{[I]}{Ki}\right)$$

where *[I]* represents simulated unbound liver concentration of each inhibitor from previously fitted and validated absorption/PBPK models. The simulated AUCs without and with the presence of an inhibitor (represented by *in vitro* K_m or adjusted apparent K_m, respectively) were used to obtain accurate estimates of DDI between omeprazole and inhibitors fluconazole and fluvoxamine.



Plasma concentration vs. time profiles of omeprazole after PO administration of 20 mg of omeprazole with placebo and 100 mg PO fluconazole

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