Prediction of omeprazole’s disposition and drug-drug interactions using a physiologically-based pharmacokinetic model

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Abstract:
A detailed model describing the absorption and pharmacokinetics of omeprazole and its main metabolites, hydroxyomeprazole and omeprazole sulphone, was built using SimuProPLUS (Simulations Plus, Inc.). The program’s Advanced Compartmental and Transit (ACTR) model described the absorption; the pharmacokinetics of all compounds was simulated with a physiologically-based pharmacokinetics (PBPK) model. The metabolic clearance of omeprazole and its metabolites in gut and liver was estimated from in vitro enzyme kinetic constants for CYP3A4, 2C9 and 2C19 combined with in vivo values for the distribution of 344 in gut and the average expressions of all three enzymes in liver or fitted to observed in vivo plasma concentration-time (Cp-time) profiles. The model accurately described pharmacokinetics of each compound after different intravenous (IV) and oral (PO) doses of omeprazole in different populations of subjects. The model was then used to predict the effect of fluvoxamine on the pharmacokinetics of omeprazole in extensive and poor metabolizers, accounting for varying contributions of the hydroxyomeprazole and omeprazole-metabolite drug-drug interactions in each group of subjects.

Dose-dependency of omeprazole’s pharmacokinetics:

Pharmacokinetics of omeprazole (red) and its two main metabolites, hydroxyomeprazole (blue) and omeprazole sulphone (magenta), after increasing doses of buffered PO solution of omeprazole in Western subjects. The subjects in this study were not genotyped and a general population of extensive metabolizers with respect to CYP 2C9 was assumed. Simulated Cp-time profiles (solid lines) showed good agreement with reported [3] in vivo profiles (points) for all doses and compounds. A single absorption/pharmacokinetic model was used in simulations for all three doses.

Effect of dosing route on omeprazole-metabolite DDI:

Since omeprazole’s metabolites are eliminated by the same enzymes as omeprazole, it is expected that omeprazole and its metabolites will act as competitive inhibitors of each other in vivo. Simulations exploring this effect were performed with IV as well as PO dosing. All simulations utilized the baseline model as optimized against different PO doses and adjusted for individual populations: different expression levels of CYP enzymes in Japanese vs. Western population and different 2C9 Km values for extensive and poor metabolizers. Homozygous extensive metabolizers (Het EM) were simulated well with the Km values from the baseline model. For homozygous extensive metabolizers (Het EM) all 2C9 Km values were decreased by 25% and for poor metabolizers (PM) all 2C9 Km values were increased 10-fold.

The plots on the left show the simulated effects of competitive interactions between omeprazole and its main metabolites after PO dosing in Western subjects. AUCs of omeprazole and omeprazole sulphone increased by about 20% and 40%, respectively, due to competition for CYP 2C9. The AUC of hydroxyomeprazole decreased by ~6% (red – omeprazole, blue – hydroxyomeprazole, magenta – omeprazole sulphone, solid lines – simulated Cp-time profiles, points – in vivo Cp-time profiles [1]). One of the possible explanations for the different magnitudes of these interactions after IV and PO dosing is the effect of gut metabolism. After PO dosing, a significant amount of the omeprazole sulphone metabolite may be formed by CYP 3A4 in gut before parent omeprazole is metabolized by CYP 2C9 in liver. The metabolite is then able to compete with omeprazole for CYP 2C9 binding sites immediately after both compounds reach liver. After IV dosing, omeprazole sulphone is only formed in liver, resulting in a shift between the time when the parent omeprazole is first metabolized by CYP 2C9 and the time when the omeprazole sulphone metabolite accumulates to a sufficient degree to affect omeprazole’s metabolism. This hypothesis is under further investigation.

Effect of fluvoxamine on pharmacokinetics of omeprazole:
The effect of fluvoxamine on the PK of omeprazole and its metabolites was predicted through dynamic simulation of the coadministration of omeprazole and fluvoxamine using an omeprazole model validated against data from IV dosing in Japanese subjects (as shown above). 40 mg of omeprazole was administered PO on the 7th day of 25 mg fluvoxamine dosing of fluvoxamine. As expected based on the IV data, the predicted interaction was the same for homoygous and heterozygous EMs; however, the observed DDI [5] was higher for heterozygous EMs due to the lower AUC in this group of subjects after administration of omeprazole alone. This might be due to different subjects being used in each study and contributions of other physiological factors than just the CYP 2C9 genotype.

The plots on the left show the results of simulations incorporating the competitive interactions in different groups of Japanese subjects after IV dosing of omeprazole irrespective of genotype, the interactions did not have a significant affect on the AUC of omeprazole or hydroxyomeprazole (both compounds showed 1-2% change in AUC within 6 h). A slightly higher change in the AUC of omeprazole sulphone was observed, where the simulations with interaction showed up to 20% increase in this metabolite’s AUC compared to simulations without interaction. The largest effect was observed for the group of homozygous extensive metabolizers (Het EM). Only ~2% increase in sulphone’s AUC was observed in the group of poor metabolizers (PM). (red – omeprazole, blue – hydroxyomeprazole, magenta – omeprazole sulphone, solid lines – simulated Cp-time profiles, points – in vivo Cp-time profiles [4]).

Conclusions:
A single model was able to account for the pharmacokinetics of omeprazole and its metabolites in different populations (after accounting for physiological differences between populations). This comprehensive mechanistic model was used to explore the effects of individual compounds within the metabolic pathway on each other’s pharmacokinetics as well as the effect of another compound (fluvoxamine) on their pharmacokinetics. Differences in DDI potential after different routes of administration and in different populations were also evaluated. Further uses of the model would include estimation of DDI potential for different dosing regimens of omeprazole and a second compound (administered simultaneously or with a certain time shift, etc.) to help with specifying recommendations for dosing in clinic.

References:
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