Title: PK-PD Modeling using 4β-Hydroxycholesterol to Predict CYP3A Mediated Drug Interactions

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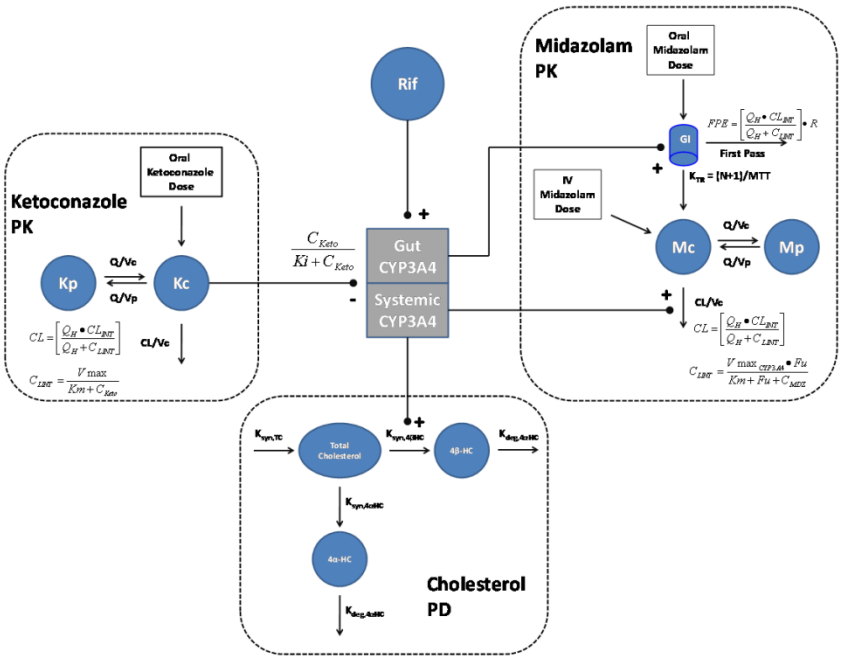
Objectives: Develop a semi-mechanistic PK-PD model model for the effects of rifampin and ketoconazole on CYP3A mediated formation of plasma 4β-hydroxycholesterol.

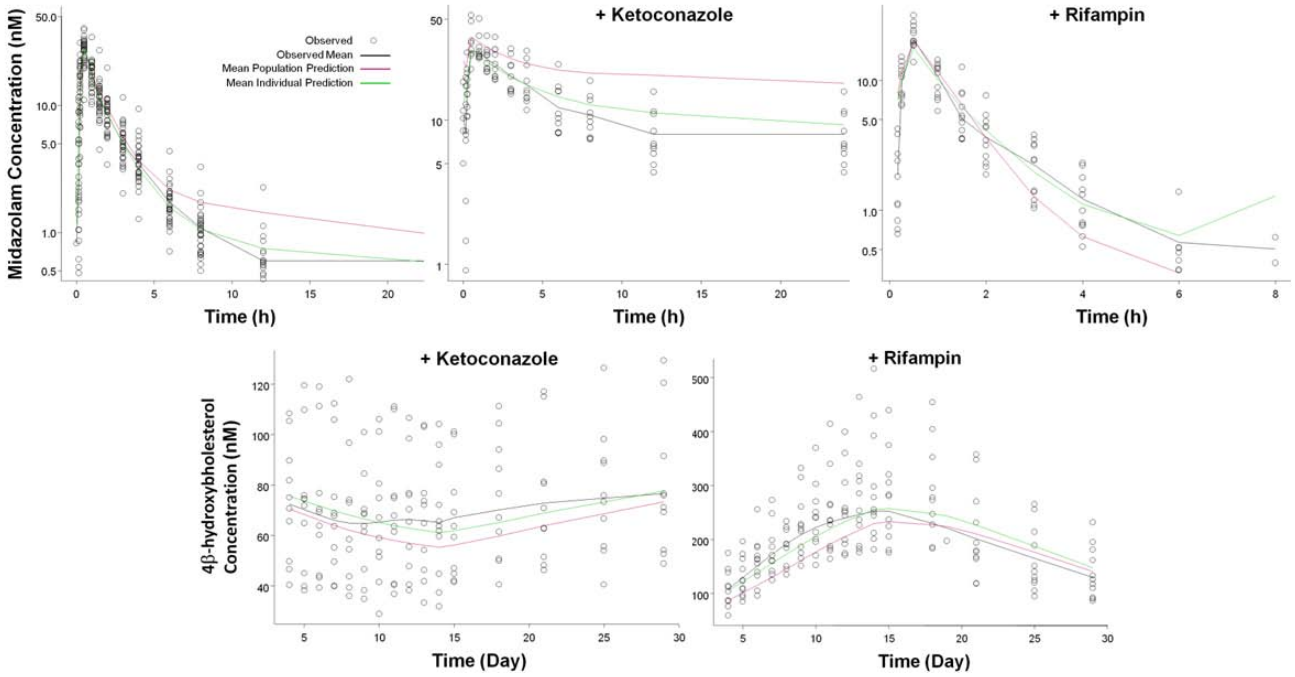
Methods: PK and PD data from a clinical study of the effects of rifampin and ketoconazole on the metabolism of endogenous markers of CYP3A4 activity, and on midazolam PK in healthy subjects was used in the analysis. The data included midazolam PK, plasma total cholesterol, plasma 4β-hydroxycholesterol, and 4α-hydroxycholesterol. Model development was conducted via an MCMC Bayesian estimation approach with informative priors (Figure 1), helping to overcome the lack of availability of PK data for ketoconazole and rifampin. Convergence of the model parameters and objective function was evaluated by visual inspection of the "caterpillar" plots for three independent MCMC chains and by examination of the Gelman & Rubin statistics. Thirty thousand iterations of each MCMC chain were used during the burn-in phase, and one thousand for the stationary phase. Additional evaluation of model was conducted by visual inspection of the predictions with the observed data, and comparison of predicted vs. observed summary PK measures.

Figure 1. CYP3A PK-PD model



Results: The three MCMC chains appeared to converge to the same objective function value and parameter estimates based on the Gelman & Rubin statistics and visual inspection of the "caterpillar" plots. The upper bound of the 95% confidence interval for the Gelman & Rubin shrink factor for the objective function value was 1.33, while for the fixed effect parameters it 1.11. Separate parameters were required for induction of CYP3A in the gut (~ 30-fold) relative to liver (~ 3.4-fold), and for ketoconazole's Ki for midazolam (~ 0.14 nM) vs. 4β-hydroxycholesterol (~ 50 nM). The PK-PD model was effective in predicting the time course of plasma midazolam and 4β-hydroxycholesterol levels under conditions of CYP3A inhibition and induction (Figure 2). The model was also effective in estimating the change in oral and IV midazolam AUC in the presence of ketoconazole, and the change in oral midazolam AUC in the presence of rifampin. However, the effect of rifampin on the AUC of IV midazolam was under-predicted.

Figure 2. Observed and predicted midazolam and 4β-hydroxycholesterol vs. time.



Conclusions: A semi-mechanistic PK-PD model was developed to describe the effect of ketoconazole and rifampin on midazolam PK and plasma 4β-hydroxycholesterol levels. This model will facilitate incorporation of 4β-hydroxycholesterol as a biomarker of CYP3A modulation in future clinical studies.