INVESTIGATING THE IMPACT OF ENZYME CORRELATIONS ON INTER-INDIVIDUAL VARIABILITY IN PHARMACOKINETICS AND DRUG-DRUG INTERACTIONS

O Hatley[1], U Ezuruike[1], J Wedagedera[1], R Takahashi[2], J Mao[2], I Gardner[1]

1.Certara UK (Simcyp Division), Sheffield, S1 2BJ, United Kingdom, 2.Genentech, Inc., A Member of the Roche Group, San Francisco, CA, USA

P214

Background

The generation of virtual individuals for physiologically based pharmacokinetic (PBPK) modelling often employs correlations of covariates to generate realistic physiological system parameters and incorporate known sources of inter-individual variability in drug exposure[1]. Extensive meta-analysis of cytochrome P450 (CYP) abundances based on western blot analysis have been published and used in mechanistic PBPK models[2]. However, blotting has been rarely employed to look at multiple enzyme abundances within the same individual due to the technical challenges of the technique and the large sample requirements. The emergence of LC-MS/MS technologies for quantifying enzyme abundance in biological samples enables multiple enzymes to be measured in the same individual, allowing for relationships between different metabolic enzymes to be investigated. A Cholesky matrix (based on a database from 22 donors[3]) was incorporated into the Simcyp Simulator (from V17) to enable multiple correlations between hepatic CYP enzymes to be described. The aim of this work is to compare the impact of independently sampled CYP distributions *vs.* using enzyme correlations within PBPK models on the simulated pharmacokinetic and drug-drug interaction (DDI) variability for compounds that are substrates for multiple CYP enzymes.

Methods

Populations of 10x100 virtual Sim-Healthy Volunteers were simulated in the Simcyp Simulator V18R1, comparing independently sampled CYP distributions *vs.* using the reported enzyme correlation[3]

Repaglinide (CYP 2C8, 3A4 and OATP 1B1 substrate) and Sildenafil (CYP 2C9 and 3A4) were selected as investigational compounds. The impact of enzyme correlations on DDIs was investigated using co-administered 200 mg Ketoconazole (strong CYP 3A4 inhibitor), or 600 mg Gemfibrozil and its metabolite (Gemfibrozil 1-O-β-Glucuronide) (CYP 2C8/9 & OATP 1B1 inhibitors).

In addition, a sensitivity analysis was conducted in a virtual population of 10x35 Sim-Healthy Volunteers to look at DDI liability and variability in populations with or without enzyme correlations as the fraction metabolised (fm) by the inhibited enzyme was varied.

Results

Comparisons of using independently sampled distributions *vs.* enzyme correlations are shown in Figure 1. The correlation between CYP 2C8 and 3A4 (Figure 1B) and CYP 2C9 and 3A4 (Figure 1D) were 0.49 and 0.17, respectively.

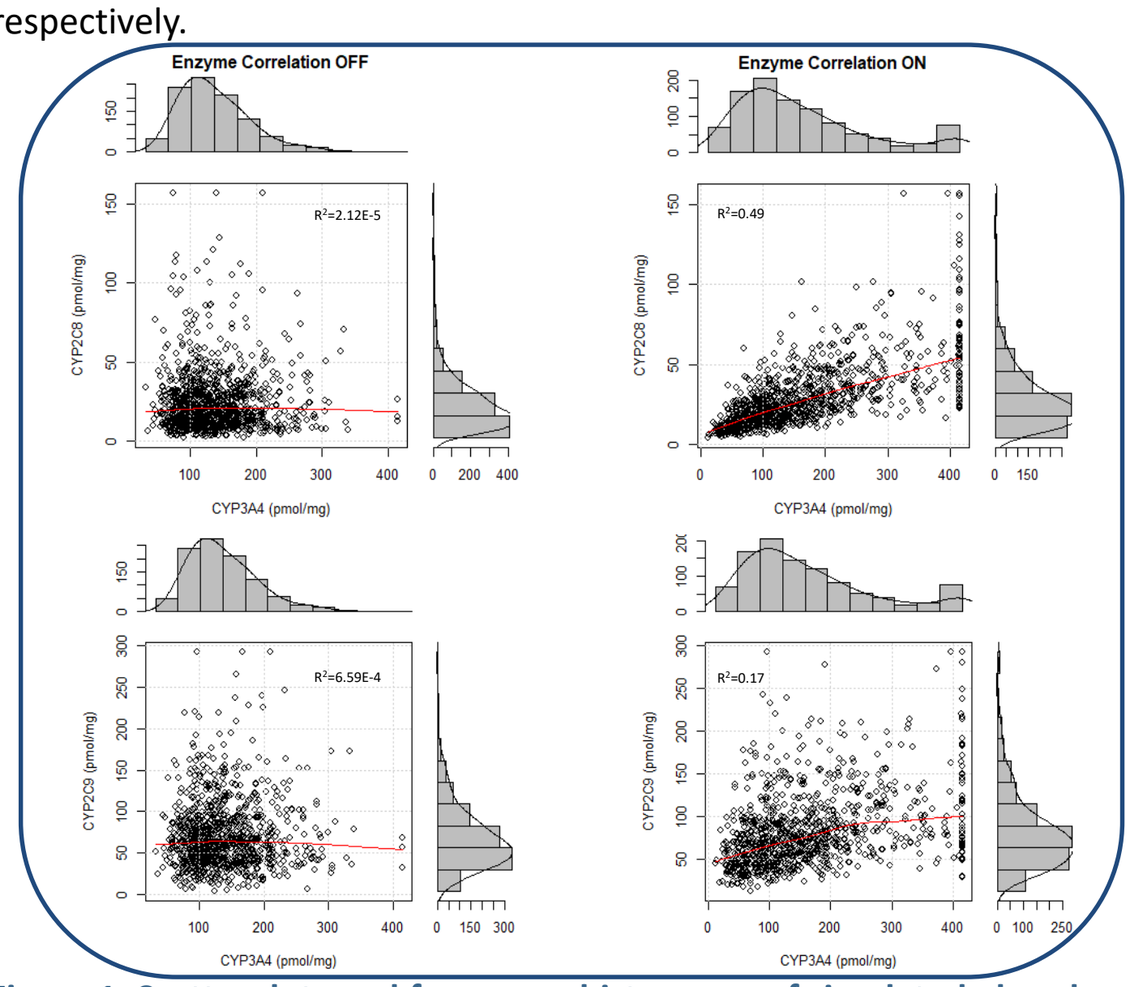

Figure 1. Scatterplots and frequency histograms of simulated abundances of CYP 3A4 *vs.* CYP 2C8 and CYP 3A4 *vs.* CYP 2C9 in 1000 virtual individuals with and without assuming enzyme correlation

Results continued

Comparisons to observed repaglinide DDIs using simulations with and without enzyme correlations for gemfibrozil and ketoconazole showed slight improvements in predictions of observed data (Table 1). Observed data was not available for sildenafil for comparison.

Table 1. Comparison of observed and predicted repaglinide DDIs using the assumption of CYP 3A4 and CYP 2C8 no correlation and with correlation. geomean (90%CI)

DDI	Observed	No correlation	Correlation
Repaglinde:Gemfibrozil	5.0 (4.3-5.7)[4]	3.93 (3.77-4.10)	4.23 (3.95-4.28)
Repaglinde:Ketoconazole	1.15 (0.87-1.53)[5]	1.55 (1.49-1.62)	1.41 (1.38-1.45)

Simulated fm for CYP3A4 for repaglinide and sildenafil was 0.35 and 0.85, respectively. Sensitivity analysis on fm showed Including enzyme correlations in the PBPK model increased variability in repaglinide control and inhibited exposure (Figure 2 A&B). The predicted DDI variability with ketoconazole (mean and SD) when CYP 3A fm was >0.25 was slightly reduced (Figure 2D). The simulated variability in Sildenafil exposure was also increased when enzyme correlations were considered (not shown). The variability in DDI with ketoconazole increased when the CYP 3A4 fm was >0.5. Gemfibrozil DDI variability was unchanged by using enzyme correlations for either substrate.

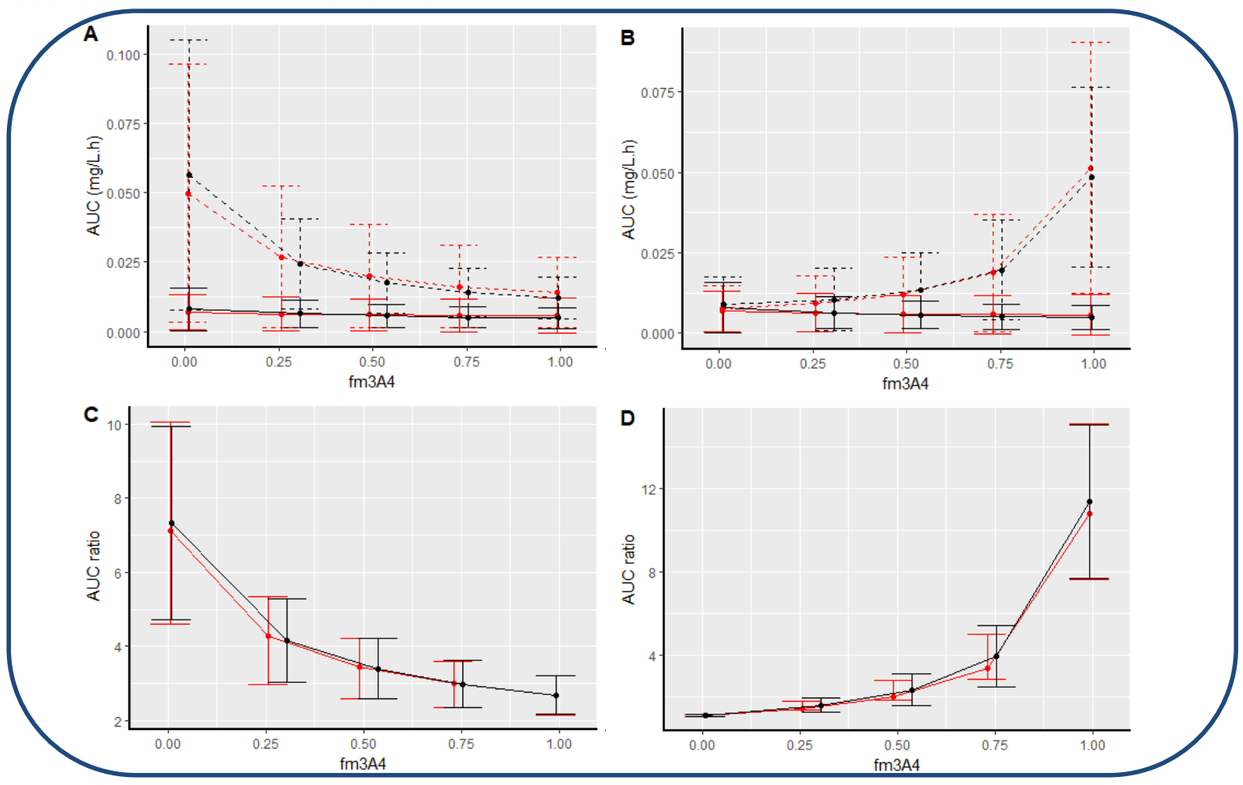

Figure 2. Sensitivity analysis (mean and SD) of CYP3A4 fm in AUC and AUC ratio for repaglnde:gemfibrozil (A and C) and repaglinde:ketoconazole (B and D) interactions. The fm of CYP3A4 and CYP2C8 were altered to keep total metabolic contribution the same in each simulation. Each simulation represents 10x35 Sim-Healthy volunteers (20-50 years, 50% female). Red lines: correlation, black: no correlation. Dashed lines: inhibited AUC

Conclusions

- Enzyme correlations impact substrates for multiple enzymes, resulting in increased variability in exposure, resulting from individuals with low or high abundances for both enzymes.
- The impact on DDI variability may depend on the enzyme involved, extent of inhibition and the relative fm contribution.
- Further work will focus on investigating the impact of the multiple-CYP correlation approach for other known multiple enzymes substrates, time-dependant or induction DDIs (i.e. after multiple doses), and the impact of using larger datasets of enzyme abundance correlations.

References

1. Jamei M *et al.,* AAPS J. 2009;11(2):225-37.
2. Rowland Yeo K *et al.,* Br J Clin Pharmacol. 2004;57(5):687.
3. Achour B, *et al.,* Drug Metabolism and Disposition,2014; 42:500–510.
4. Honkalammi *et al.,* Clin Pharmacol Ther. 2011;89(4):579-586.
5. Hartop *et al.,* J Clin Pharmacol. 2003 43(6):649-60.

ISSX, Portland, Oregan, 28-31 July 2019