Implications of inter-correlation between hepatic CYP3A4-CYP2C8 enzymes for the evaluation of drug-drug interactions: a case study with repaglinide and gemfibrozil

Kosuke Doki¹², Adam S. Darwich², Brahim Achour², Aleksi Tornio³, Janne T. Backman³, Amin Rostami-Hodjegan²⁴

¹Department of Pharmaceutical Sciences, Faculty of Medicine, University of Tsukuba, Japan, ²Centre for Applied Pharmacokinetic Research, University of Manchester, UK, ³Department of Clinical Pharmacology, University of Helsinki and Helsinki University Hospital, Finland, ⁴Simcyp Limited (A Certara Company), UK

Background: Statistically significant positive correlations are reported for the abundance of hepatic drug-metabolising enzymes [1]. Current population-based physiologically-based pharmacokinetic (PBPK) models do not consider inter-correlations between the abundances of different enzymes when using Monte Carlo simulations to generate virtual individuals.

Aim: We investigate, as an example, the impact of CYP3A4-CYP2C8 inter-correlation on the predicted inter-individual variabilities of clearance and drug-drug interactions (DDIs) for repaglinide, a substrate of CYP2C8 and CYP3A4, using PBPK modelling.

Methods: PBPK modelling and simulation was employed using Simcyp Simulator (v15.1). Virtual populations were generated assuming inter-correlations between hepatic CYP3A4-CYP2C8 abundances derived from observed values in 24 human livers [1]. A repaglinide PBPK model was used to predict pharmacokinetic parameters in presence and absence of gemfibrozil, an inhibitor of CYP2C8, in virtual populations, and the results were compared with a clinical DDI study [2].

Results: Coefficient of variation (CV) of oral clearance was 52.5% in the absence of inter-correlation between CYP3A4-CYP2C8 abundances which increased to 54.2% when incorporating inter-correlation. In contrast, CV for predicted DDI (as measured by AUC ratio before and after inhibition) was reduced from 46.0% in the absence of inter-correlation between enzymes to 43.8% when incorporating inter-correlation: these CVs were associated with 5th/95th percentiles (2.48-11.29 vs. 2.49-9.69). The range of predicted DDI was larger in the absence of inter-correlation (1.55-77.06) than when incorporating inter-correlation (1.79-25.15), which was closer to clinical observations (2.6-12 [2]).

Conclusion: The present study demonstrates via a systematic investigation that population-based PBPK modelling incorporating inter-correlation led to more consistent estimation of extreme values with those observed in inter-individual variabilities of clearance and DDI. As the inter-correlations more realistically reflect enzyme abundances, virtual population studies involving PBPK and DDI should avoid using Monte Carlo assignment of enzyme abundance.

References: