Predicting the Effect of CYP2D6 Polymorphism on Pharmacodynamic Response to Metoprolol

K. Abduljalil1, L. Gaohua1, R. Rose1, T.N. Johnson1, M. Chetty1, M. Jamei1, D. Edwards1, A. Rostami-Hodjegan1,2
k.abduljalil@simcyp.com
1-Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK
2-School of Pharmacy and Pharmaceutical Sciences, Manchester University, Manchester, UK

Background
The polymorphism of CYP2D6 enzyme is believed to be an important determinant of variation in the clinical response to standard doses of metoprolol in ultrarapid metabolisers (UMs), extensive metabolisers (EMs) and poor metabolisers (PMs). Plasma concentrations and effects on heart rate have been shown to correlate significantly with CYP2D6 metabolic phenotype in clinical studies. The prevalence of some phenotypes is not adequately high to discern the differences in PK/PD of drugs by the conduct of small clinical studies. It would be of value to use the in vitro information on metabolism together with PK/PD information in prevalent phenotypes of CYP2D6 to conduct virtual clinical studies with a view to assess the potential pharmacological differences in various less frequent phenotypes prior to conduct of any clinical studies.

Objectives
To simulate the reduction in heart rate due to a standard 100 mg dose of metoprolol in virtual healthy Caucasian populations stratified for their CYP2D6 phenotypes using the Simcyp simulator.

Methods
Simulations of metoprolol PK and the decrease in heart rate effects in UMs, EMs and PMs were performed using Simcyp V11. The default Simcyp metaboloprotein compound file was used with the first order absorption model, minimal PBPK model and elimination defined by enzyme kinetics. The PK/PD relationship was taken from Kirchheiner et al. 20041, and was assumed to be the same regardless of CYP2D6 genotype. Simulations were compared with clinical observations from two studies1,2.

Results
The simulated contribution of the CYP2D6 phenotype to metoprolol PK/PD within Simcyp is based on the propagation of the differences in CYP2D6 abundance to the PD response via changes in the plasma concentration profile. In general both PK and PD profiles were predicted successfully (Table 1). The simulated CL (Dose/AUC) of UM group is 16- and 2-fold higher than that of PM and EM groups, respectively.

Simulated mean PD profiles showed that the area under the effect curve in PMs was 6-fold higher than that in UMs, and 2-fold higher than that in EMs. The simulated/observed ratios for the maximum reduction in heart rate and absolute area under effect curve are 0.94 and 1.2 for PMs, 0.9 and 0.96 for EMs, and 0.94 and 0.73 for UMs groups, respectively.

The simulated PK & PD profiles of metoprolol are superimposed on observed data in Figure 1. These indicate the potential for prediction of genetic differences in PD once the PKPD relationship is established in wild-type genotypes.

Conclusions
The Simcyp Simulator with its PD module is a seamless tool to assess the propagation of key PK factors, such as metabolic activity or drug-drug interactions, through to a PD effect. Simulation results showed consistency with clinical observations in terms of significant differences of metoprolol PK/PD profiles between PMs and UMs with a marginal change between EMs and UMs. PMs may not achieve optimal target concentrations of metoprolol, which can lead to a lower benefit from the standard 100mg dose of the drug compared with PMs. Although POPPK studies have been valuable to inform investigators of such differences, these studies should be powered adequately to recognise the differences. Clinical trial simulations similar to the one shown in this study can be used to investigate the design of POPPK studies and their power.

References