Predicting the Effect of CYP2D6 Polymorphism on Pharmacodynamic Response to Metoprolol

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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 metoprolol 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 2004[1], and was assumed to be the same regardless of CYP2D6 genotype. Simulations were compared with clinical observations from two studies[1,2].

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.

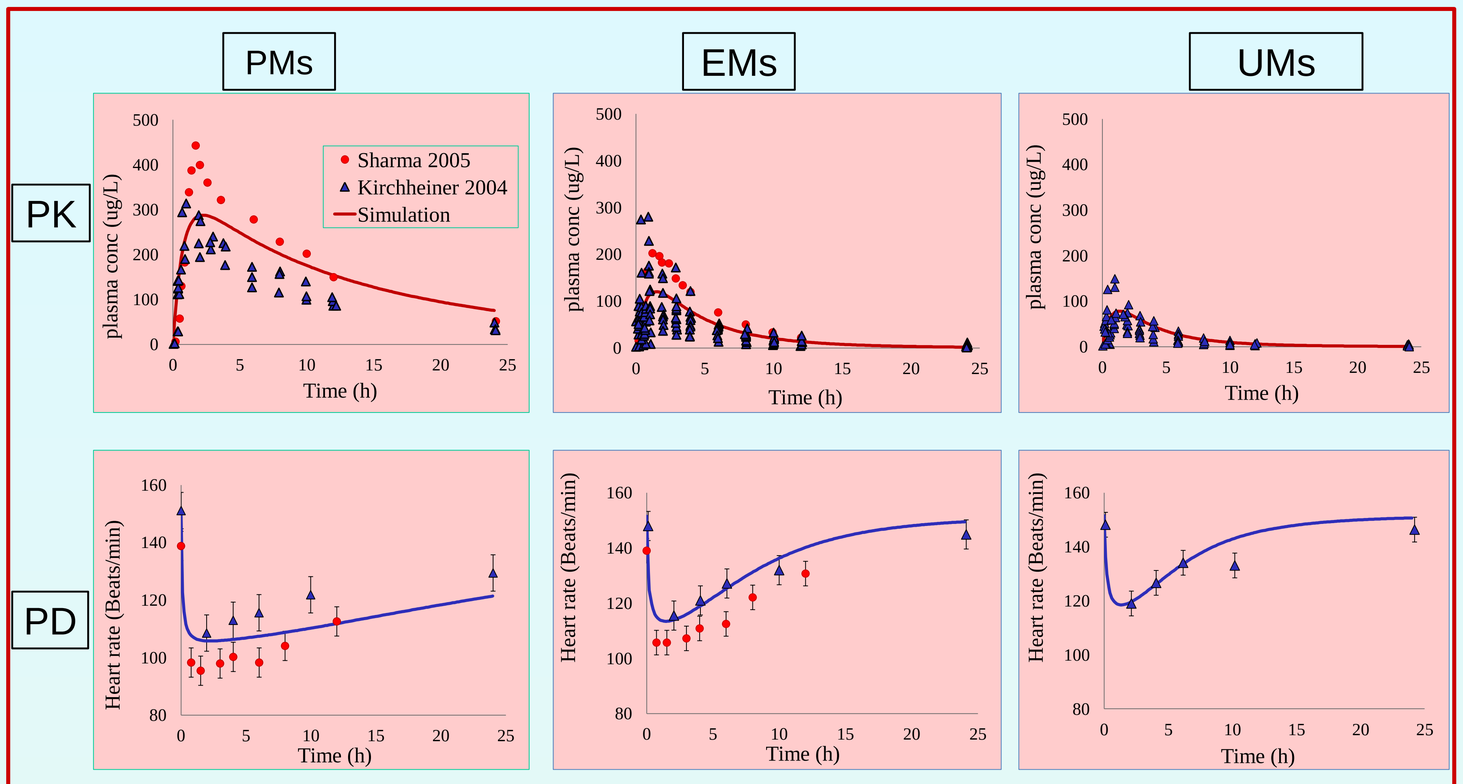

Figure 1. Metoprolol PK/PD Profile in Healthy Volunteers by CYP 2D6 Metabolizer Status

It is clear from this figure that the status of CYP2D6 phenotype has an impact on the reduction in heart rate. PMs are of particular interest as the PD effect is higher and takes longer time to return to the initial point. In comparison with EMs, and UMs, the longer action of metoprolol in PMs is a result of residence of drug in the body (see plasma concentration profile for PMs), which is caused by the lower clearance of metoprolol in PMs group. These differences indicate significant effects on metoprolol dosing in the corresponding groups of patients which could have been predicted *a priori.*

Table1. Observed vs predicted ”PRED” Metoprolol PK/PD parameters in Healthy Volunteers by CYP 2D6 Metabolizer Status.

	PM			EM			UM		
	PRED	**Observed**	**Ratio**	**PRED**	**Observed**	**Ratio**	**PRED**	**Observed**	**Ratio**
PK parameters									
AUC (ug/L/h)	4,938	3,921	***1.26***	586	839	***0.70***	304	273	***1.1***
Tmax (h)	1.82	1.63	***1.12***	1.18	1.35	***0.88***	1	1	***1.1***
Cmax (ug/L)	305	363	***0.84***	112	178	***0.63***	69	67	***1.0***
CL/F (L/h)	20	24	***0.85***	171	139	***1.22***	329	367	***0.9***
PD parameters									
Rmax (beat/min)	142	151	***0.9***	142	149	***1.0***	142	148	***1.0***
Rmin (beat/min)	103	109	***0.9***	109	116	***0.9***	113	119	***0.9***
t(Rmin) (h)	1.9	2	***1.0***	1.2	2	***0.6***	1.2	2	***0.6***
AUC (beat.h/min)[a]	831	685	***1.2***	328	363	***0.9***	223	308	***0.7***
AUC (beat.h/min)[b]	447	423	***1.1***	272	275	***1.0***			

a= reported & simulated for 24 h, b= reported & simulated for 12h

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. UMs 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

(1) Kirchheiner J et al. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2004 Oct;76(4):302-12.

(2) Sharma A et al., Modulation of metoprolol pharmacokinetics and hemodynamics by diphenhydramine coadministration during exercise testing in healthy premenopausal women. J Pharmacol Exp Ther. 2005 Jun;313(3):1172-81.