Prediction of OATP1B1-Mediated Drug-Drug Interaction Between Repaglinide and Cyclosporine Using Physiologically Based Pharmacokinetic Modelling

Karen Rowland Yeo[1], Mohsen Aarabi[2], Masoud Jamei[1], Sibylle Neuhoff[1], Geoffrey T. Tucker[1], Amin Rostami-Hodjegan[1,3]

k.r.yeo@simcyp.com

[1]Simcyp Limited, Sheffield, UK; [2]University of Medical Sciences, Gorgan, Iran; [3]The University of Manchester, Manchester, UK

Background

Cytochrome P450 (CYP) 3A4 and CYP2C8 are the main enzymes responsible for the oxidative metabolism of repaglinide (Kajosaari *et al.*, 2005a; Bidstrup *et al.*, 2003). The area under the concentration-time profile (AUC) of repaglinide is increased markedly in homozygous carriers of the *SLCO1B1* 521T>C (Val174Ala) single nucleotide polymorphism, suggesting that it is a substrate of the *SLCO1B1*-encoded hepatic uptake transporter organic anion transporting polypeptide 1B1 (OATP1B1) (Niemi *et al.*, 2005).

Plasma concentrations of repaglinide are moderately increased by drugs that inhibit CYP2C8 or CYP3A4 (Niemi *et al.,* 2004; Hatorp *et al.,* 2003). However, cyclosporine, a potent inhibitor of both OATP1B1 and CYP3A4, increased the plasma concentrations of repaglinide by 2.4 fold (Kajosaari *et al.*, 2005b).

Aim

To predict the inhibitory effect of cyclosporine on the OATP1B1-mediated hepatic uptake of repaglinide using physiologically based pharmacokinetic (PBPK) modelling.

Methods

Prior *in vitro* information for repaglinide (Table 1) were incorporated into the permeability-limited hepatic uptake module (Figure 1) of the PBPK model within the Simcyp Simulator (Version 10.1) to generate concentration-time profiles of repaglinide.

While there are *in vivo* data to support the involvement of OATP1B1 in the hepatic uptake of repaglinide (Niemi *et al*., 2005), *in vitro* parameters describing this transport are not available. Using the mean *in vivo* concentration-time profile data of Kajosaari *et al.* (2005b) and fixing all of the prior *in vitro* data, an iterative fitting procedure in the Parameter Estimation (PE) module of the Simcyp Simulator was used to obtain an estimate of 176 µl/min/million cells for the OATP1B1-mediated hepatic uptake clearance of repaglinide.

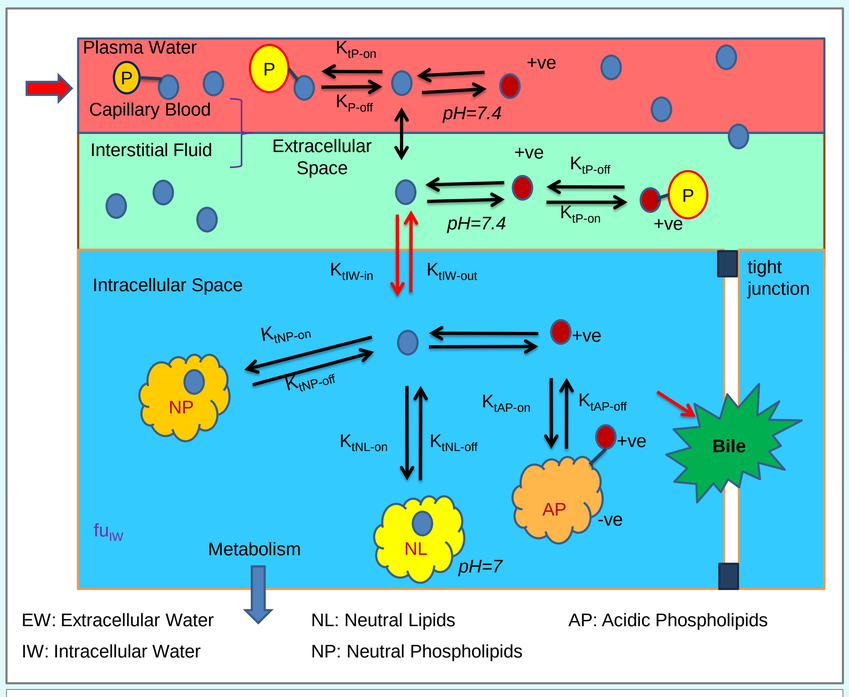

Figure 1. Permeability-Limited Model (Liver) Unbound concentrations of repaglinide in the EW and IW compartments were used as the driving forces for OATP1B1-mediated hepatic uptake and metabolism of repaglinide, respectively.

Results

Improved recovery of the *in vivo* data was observed when hepatic uptake via OATP1B1 (176 µl/min/million cells) was included in the model (Figure 2A). Simulated plasma repaglinide concentration time profiles for a single oral dose of 0.25 mg repaglinide administered before and after 2 doses of cyclosporine (100 mg) are shown in Figures 2A and 2B, respectively. Mean predicted values and ratios of C_{max} and AUC for each trial and the corresponding mean observed values (Kajosaari *et al.,* 2005a) are shown in Table 2. The predicted magnitude of interaction was negligible when inhibition of OATP1B1 was not considered.

The predicted mean plasma C_{max} values of cyclosporine for the 10 trials ranged from 645 to 777 ng/ml (mean – 711 ng/ml); the observed value was 664 ng/ml (Kajosaari *et al.,* 2005a). The predicted increase in exposure of repaglinide after 2 doses of cyclosporine is highly correlated ($r=0.7$, $p<0.05$) with cyclosporine $AUC_{(0\text{-}12)}$, which is in agreement with observed data.

Conclusion

Application of a PBPK model combined with a fitting approach and reliable *in vitro* data, allowed reasonably accurate prediction of the OATP1B1-mediated drug-drug interaction between repaglinide and cyclosporine.

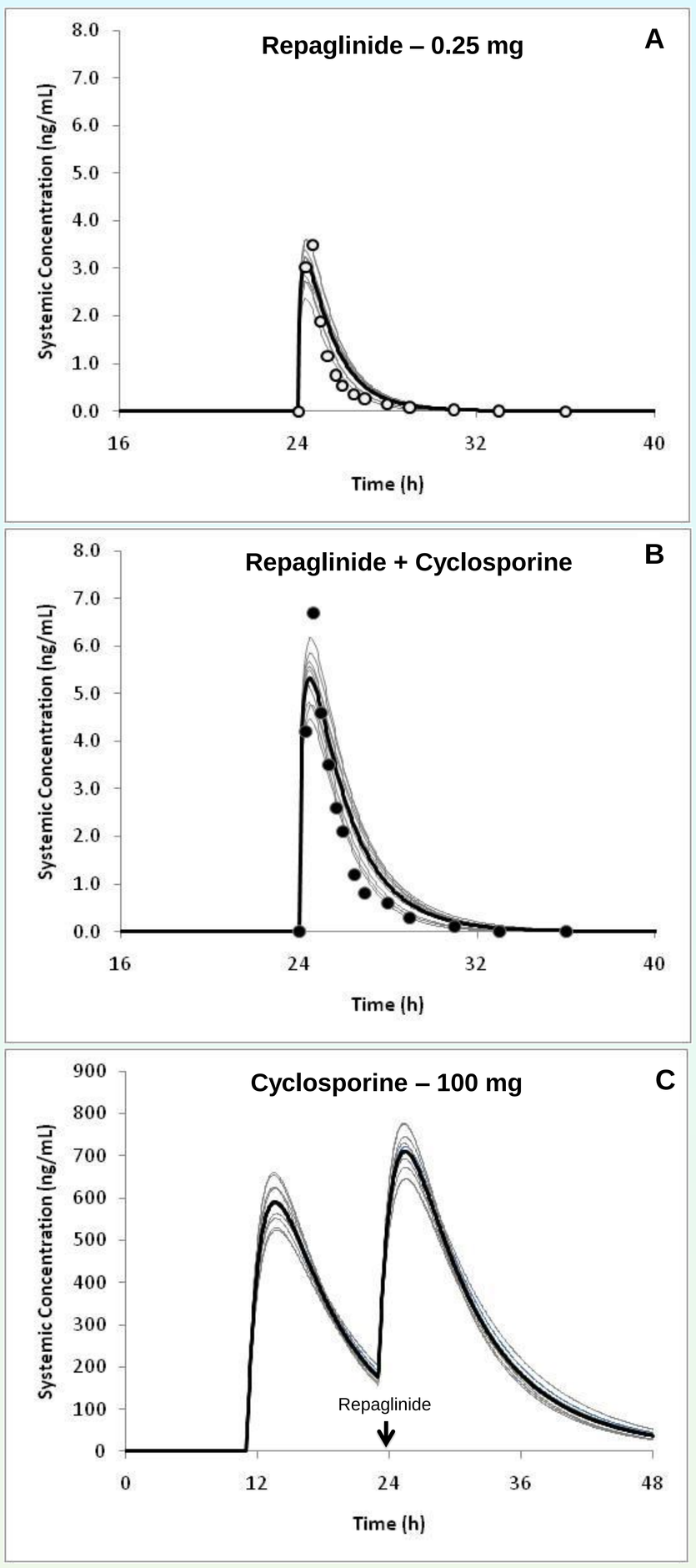

Figure 2. Simulated and observed plasma concentration-time profiles of repaglinide (0.25 mg dose) in healthy subjects before (A) and after (B) 2 doses of 100 mg cyclosporine (C) given at 12 and 24h. The grey lines represent individual trials (10 x 12) and the solid black line is the mean of the population (n = 120). The circles are mean observed values from Kajosaari *et al.* (2005a).

Note: In vitro data for inhibition of CYP3A4 (K_i – 0.21 µM) and OATP1B1-mediated uptake (K_i – 0.01 µM) by cyclosporine were used to predict the effect of cyclosporine on the exposure (C_{max} and AUC) of repaglinide (Amundsen *et al.,* 2010).

Table 1. Input parameter values used for repaglinide

Parameter	Value	Source
Molecular weight [g/mol]	452.6	
Log P	5.04	Marvin
pKa_1, pKa_2	3.7; 5.3	Marvin
B:P ratio	0.61	van Heiningen *et al.,* 1999
fu	0.025	Hatorp *et al*., 2003
PSA [Å^2]	79	Marvin
fa	1	assumed
ka (h^{-1})	2.33	Niemi *et al*., 2004
Q_{gut} (L/h)	12.2	Predicted
V_{ss} (L/kg)	0.23	Predicted

Table 2. Mean predicted and observed C_{max} and $AUC_{(0\text{-}\infty)}$ values of repaglinide before and after administration of cyclosporine

	Control (Repaglinide 0.25 mg)		+ 100 mg Cyclosporine		Ratio	
	C_{max} ng/ml	$AUC_{(0\text{-}\infty)}$ ng.h/ml	C_{max} ng/ml	$AUC_{(0\text{-}\infty)}$ ng.h/ml	C_{max}	$AUC_{(0\text{-}\infty)}$
Mean	3.09	5.83	5.33	13.8	1.72	2.37
Trial 1	2.71	5.75	4.75	13.5	1.75	2.34
Trial 2	2.87	4.81	5.16	11.9	1.80	2.49
Trial 3	3.21	6.50	5.56	15.9	1.73	2.45
Trial 4	3.59	6.87	6.16	16.3	1.72	2.37
Trial 5	3.22	5.77	5.51	13.5	1.71	2.34
Trial 6	3.25	6.38	5.37	14.5	1.65	2.27
Trial 7	2.73	4.68	4.82	11.0	1.77	2.34
Trial 8	2.36	3.94	4.46	10.1	1.89	2.57
Trial 9	3.60	7.06	5.85	16.3	1.62	2.30
Trial 10	3.40	6.52	5.68	15.4	1.67	2.36
Observed	3.90	4.40	6.70	10.8	1.72	2.45

References

Amundsen R *et al*. D*rug Metab Dispos* 2010; 85: 1499-1504.

Bidstrup TB *et al*. *Br J Clin Pharmacol* 2003; 56: 305-14.

Hatorp V *et al*. *J Clin Pharmacol* 2003; 43: 649-60.

Niemi M *et al*. *Br J Clin Pharmacol* 2004; 57: 441-7.

Niemi M *et al. Clin Pharmacol Ther* 2005; 77: 468-78.

Kajosaari LI *et al. Basic Clin Pharmacol Toxicol* 2005a; 97: 249-56.

Kajosaari LI *et al*. *Clin Pharmacol Ther* 2005b; 78: 388-99.

van Heiningen *et al*. *Eur J Clin Pharmacol* 1999; 55: 521-525.