Interplay of transport and metabolism in the gut: Predictions of drug-drug interactions using physiologically based pharmacokinetic modelling

Neuhoff, S.[1], Rowland-Yeo, K.[1], Jamei, M.[1] and Rostami-Hodjegan, A.[1,2]

S.Neuhoff@simcyp.com

[1]Simcyp Ltd, Sheffield, UK, [2]The University of Manchester, Manchester, UK

Background

Predicting the magnitude of *in vivo* drug-drug interactions (DDIs) involving cytochrome P-450 enzymes (CYP) and transport from *in vitro* data requires accurate knowledge of the kinetics describing metabolism and transport of the substrate in the gut and liver, inhibition constants for metabolism and transport, and estimates of the inhibitor concentrations at the enzyme active site and transport locus. Although there have been many reports of reasonably successful predictions of DDIs involving competitive and time-dependent inhibition, this is not the case for transporters. The recent update of regulatory guidance relating to transporters has led to increasing interest in assessing the above approach for prediction of transporter-mediated DDIs.

Aim

To investigate the effect of increasing dose on the P-glycoprotein (P-gp) mediated efflux of quinidine.

To determine the relative importance of CYP3A4 and P-gp in the drug-drug interaction between quinidine and verapamil.

Method

Prior *in vitro* information on the metabolism, permeability and P-gp efflux kinetics of quinidine were combined with physicochemical data in the Simcyp Population-based Simulator to generate concentration-time profiles of quinidine over a dose range of 10 to 2000 mg to assess the dose-dependent effect on metabolism and P-gp efflux. A whole-body physiologically based pharmacokinetic (WB-PBPK) approach including the Advanced Dissolution, Absorption and Metabolism (ADAM) model and incorporating variability was applied (Jamei *et al.*, 2009). Where possible (*i.e.*, at 200, 400 and 600 mg), predicted data were compared with corresponding observed data.

In vitro data relating to inhibition of CYP3A4 and P-gp efflux by verapamil were then used to investigate the effect of verapamil on the systemic exposure of quinidine assuming 3 sets of conditions: mechanism based inhibition of CYP3A4-mediated metabolism of quinidine only, inhibition of P-gp efflux only and inhibition of both CYP3A4 metabolism and P-gp efflux.

Results

Pharmacokinetic (PK) studies in healthy volunteers (HV) were identified from the literature (Table I).

Table I: PK-studies for Quinidine in Healthy Volunteers

Reference	formulation (company)	dose [mg]	application	population	N (m/f)	age [Y]
Damkier *et al.*, 1999	quinidine sulphate (Kinidin "Dak", Nycomed DAK)	200	single dose	HV, Caucasian	6 (6/0)	not stated
Edwards *et al.*, 1987	quinidine sulphate (Parke-Davis)	400	single dose	HV, Caucasian	6 (6/0)	23-34
Bleske *et al.*, 1990	quinidine sulphate (Warner Chilcott, Morris Plains, NJ)	400	single dose	HV, Caucasian	8 (8/0)	22-34
Min *et al.*, 1996	quinidine sulphate (Roxane, Columbus)	400	single dose (2 x 200 mg)	HV, Caucasian	12 (12/0)	not stated
Wooding-Scott *et al.*, 1988	quinidine sulphate (brand not given)	400	single dose (2 x 200 mg)	HV, Caucasian	6 (6/0)	22-35
Ho *et al.*, 1999	quinine sulphate (Quinoc-F, Douglas Pharmaceuticals, Auckland, New Zealand)	600	single dose (2 x 300 mg)	HV, (2 Chinese, 2 Indians, 6 Caucasians)	10 (10/0)	19-37

The simulated concentration-time profiles of quinidine were reasonably consistent with observed data (mean and associated variability) across 6 independent studies at 3 different doses (Figures 1 and 2).

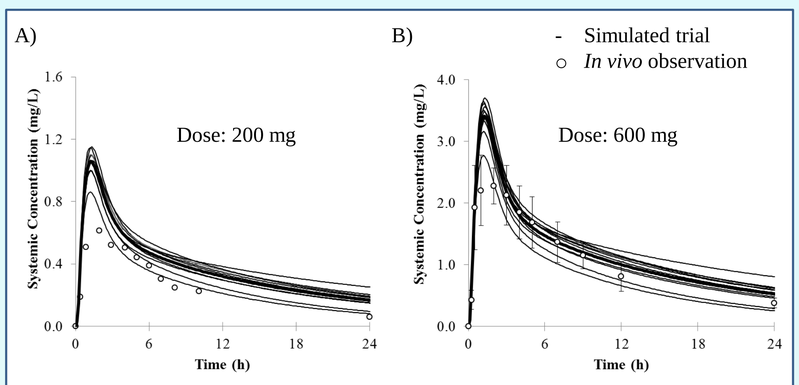

Figure 1 *- Simulated plasma concentration-time profiles of quinidine after an oral dose of 200 mg (A) and 600 mg (B). The thin lines represent individual trials (10 x 10) and the solid black line is the mean of the population (n = 100). The circles are mean observed values considering the inhibition of P-gp efflux.*

Across the four studies involving the 400 mg dose, there was considerable variability across the *in vivo* studies (Figure 2).

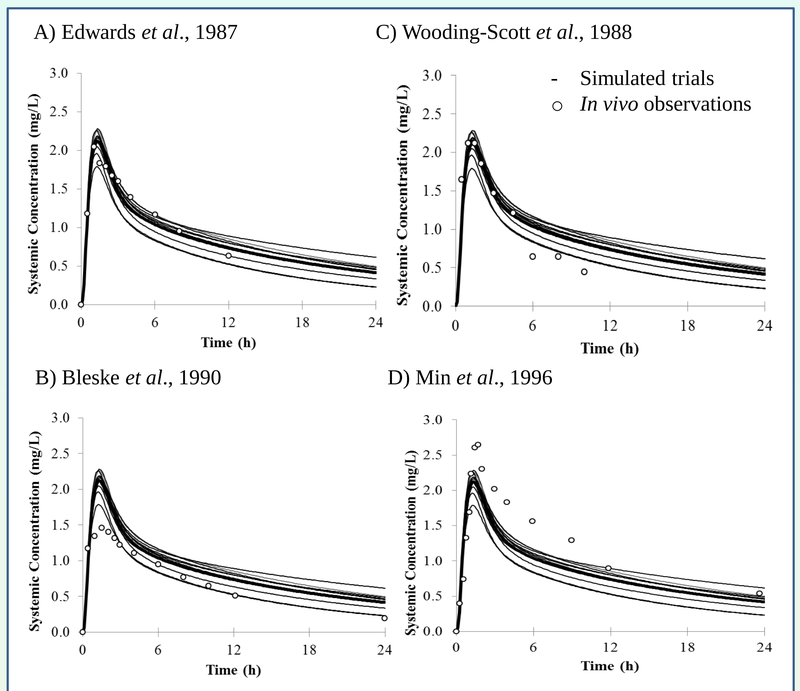

Figure 2 *– Simulated plasma concentration-time profiles of quinidine after an oral dose of 400 mg. The thin lines represent individual trials (10 x 10) and the solid black line is the mean of the population (n=100). The circles are mean observed values.*

Although the impact of P-gp-mediated efflux on the exposure of quinidine appeared to be relatively small, a dose-dependent effect on the relative contribution of the transporter mediated component to the overall disposition of the compound was observed (Figure 3, Table II).

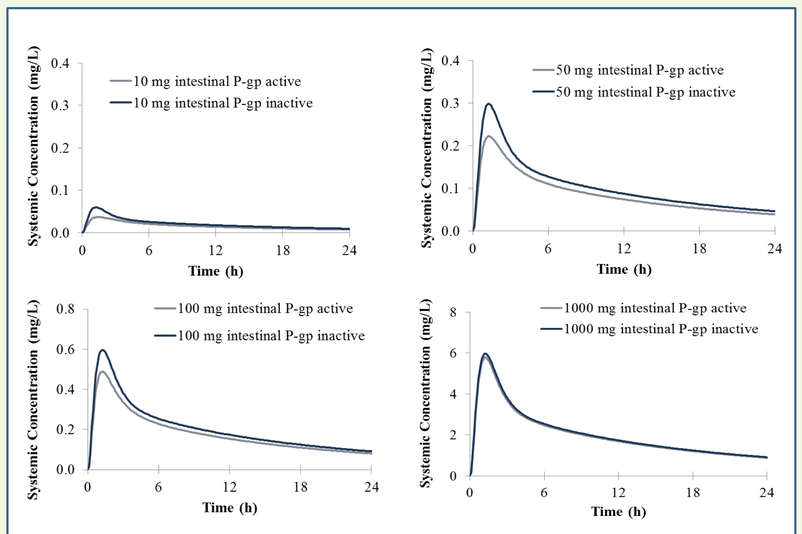

Figure 3 *– Mean values of simulated plasma concentration-time profiles of quinidine after an oral dose of 10, 50, 100 or 1000 mg in a population of 100 individuals with and without consideration of the inhibition of P-gp efflux over time.*

Table II: Median simulated AUC and Cmax of Quinidine in HV

	AUC [mg/L.h]			Cmax [mg/L]		
Dose [mg]	w/o P-gp	with P-gp	ratio	w/o P-gp	with P-gp	ratio
10	0.49	0.37	1.34	0.06	0.04	1.64
25	1.24	0.97	1.28	0.15	0.10	1.54
50	2.48	2.02	1.23	0.31	0.22	1.39
75	3.71	3.19	1.16	0.46	0.36	1.31
100	4.95	4.33	1.14	0.62	0.50	1.24
200	9.90	8.9	1.11	1.24	1.08	1.14
400	19.8	18.9	1.05	2.47	2.28	1.09
600	29.7	28.9	1.03	3.71	3.47	1.07
1000	49.5	48.6	1.02	6.18	5.92	1.04
2000	99.0	97.9	1.01	12.4	12.1	1.02

Predicted increases in the systemic exposure of quinidine during co-administration of verapamil indicated that inhibition of P-gp was negligible compared to mechanism based inhibition of CYP3A4. A comparison of predicted versus observed data, with respect to change in systemic exposure, indicated that the performance of the model was improved when only CYP3A4 inhibition was considered (Figure 4).

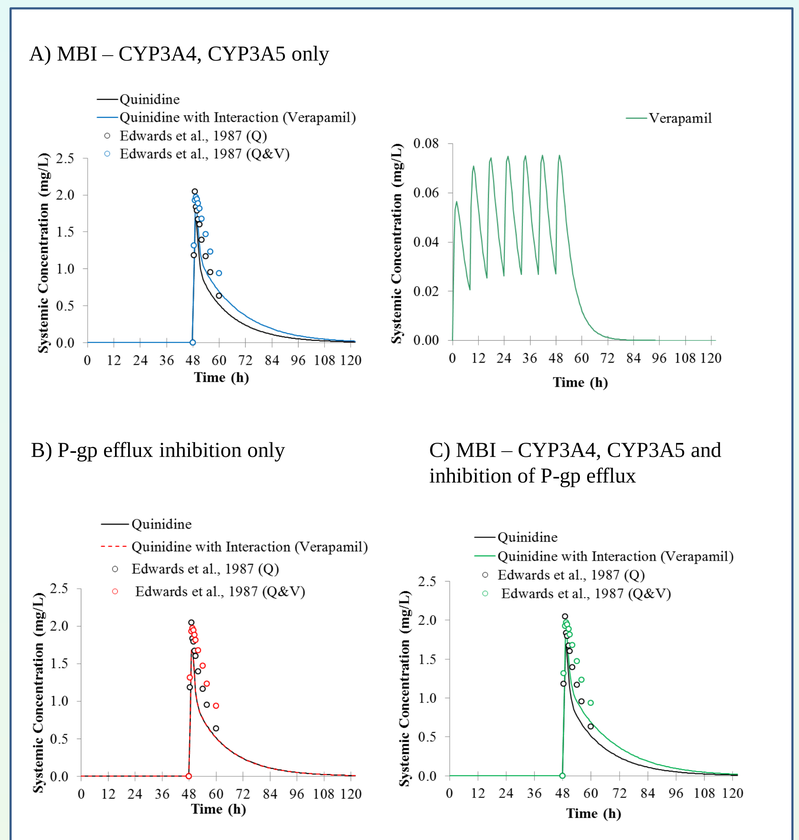

Figure 4 *- Values of simulated systemic concentration in plasma of quinidine considering the effects of verapamil for a Population Representative. Three sets of conditions are investigated: (A) mechanism based inhibition of CYP3A4-mediated metabolism of quinidine only, (B) inhibition of P-gp efflux only and (C) inhibition of both CYP3A4 metabolism and P-gp efflux.*

The MBI of CYP3A dominates the interaction, while the inhibition of P-gp seems for the highly permeable Biopharmaceutical-classification System (BCS) I compound, quinidine, negligible.

Conclusion

Application of a WB-PBPK approach in conjunction with reliable *in vitro* data on metabolism and transporters, allows elucidation of the interplay between metabolic and transporter components that may contribute to the disposition of a drug.

References

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