PREDICTION OF THE INCREASE IN SYSTEMIC EXPOSURE OF PAROXETINE IN PATIENTS WITH RENAL IMPAIRMENT

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Introduction

Renal impairment (RI) not only affects elimination of drugs in the kidney, but also the non-renal route of drugs, such as paroxetine that are extensively metabolised in the liver. Renal failure may influence hepatic drug metabolism either by inducing or suppressing hepatic cytochrome P450 (CYP) enzymes, by interfering with transporter mediated uptake into the liver, or by its effects on other variables such as protein binding. One of the main mechanisms contributing to these effects, appears to be the accumulation of uraemic toxins in RI, which can modulate CYP activity.

The objectives of this study were to incorporate such changes in a physiologically based pharmacokinetic (PBPK) model to predict the increase in exposure of paroxetine in subjects with RI relative to healthy volunteers (HV).

Methods

Prior *in vitro* and *in vivo* information on the metabolism and kinetics of paroxetine (Jornil *et al.*, 2010) were used to assess whether predicted concentration-time profiles in HV were consistent with *in vivo* data (Sindrup *et al*., 1992). Data relating to changes in CYP abundance, protein binding, renal function, tissue composition and blood flows in subjects with varying degrees of RI were collated from the literature (Table 1). These data were incorporated into the Simcyp Simulator (Version 10) to predict the increase in exposure (AUC and C_{max}) in subjects with RI relative to HV (Doyle *et al.,* 1989).

Table 1. Key physiological and biochemical parameter changes associated with differing degrees of renal impairment

Parameter		GFR (ml/min/1.73 m²)		
		Control	30-59	<30
CYP1A2 (pmol/mg)		52	33	24
CYP2C8 (pmol/mg)		24	20	13
CYP2C9 (pmol/mg)		73	63	29
CYP2C19 (pmol/mg)		14	5.5	2.3
CYP2D6 (pmol/mg)		8.0	4.6	2.1
CYP3A4 (pmol/mg)		137	73	62
Albumin ($g.L^{-1}$)	M	44.9	41.6	37.6
	F	41.8	38.8	35.0
Haematocrit (%)	M	43.0	39.7	36.5
	F	38.0	33.2	31.3
Gastric emptying time (h)		0.40	0.55	0.65

Results

Simulated concentration-time profiles of paroxetine in HV were consistent with *in vivo* data during single and multiple dosing (30 mg once daily; Figure 1). Predicted fold increases in exposure for subjects with RI relative to HV were reasonably consistent with observed data (Figure 2). After 14 days of dosing with 30 mg paroxetine once daily, predicted fold increases in C_{max} and AUC on the last day of dosing were reduced; values were 1.3 and 1.6, respectively, for subjects with severe RI.

Conclusions

Prior simulation of the potential exposure of individuals with RI using PBPK models incorporating disease specific changes may help in the selection of a safe and effective dosage regimen.

References

Sindrup *et al.* Clin Pharmacol Ther 1992; 51: 278-87

Doyle *et al.* Acta. Psychiatr. Scand 1989; 80:89-90

Jornil et al. Drug Metab Dispos *2010;* 38(3): 376-385.

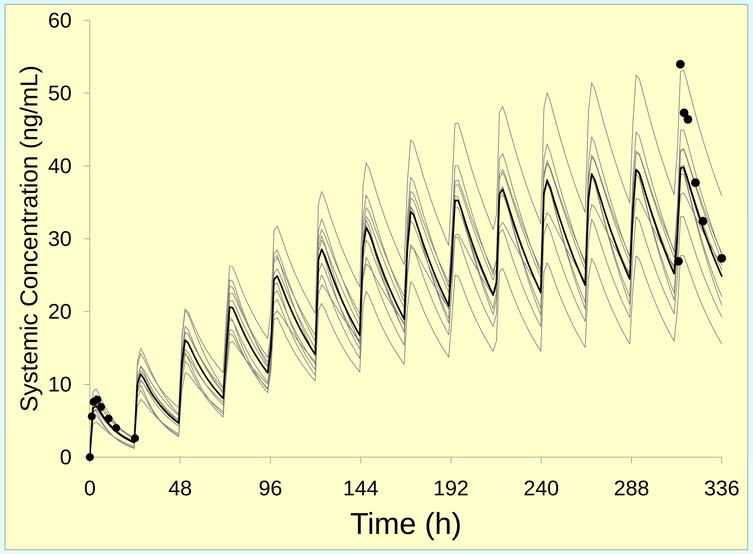

Figure 1. Simulated plasma concentration-time profiles of paroxetine after dosing of 30 mg once daily for 14 days in HV. The grey lines represent individual trials (10 x 6) and the solid black line is the mean of the population (n = 60). The circles are mean observed values (Sindrup *et al*., 1992).

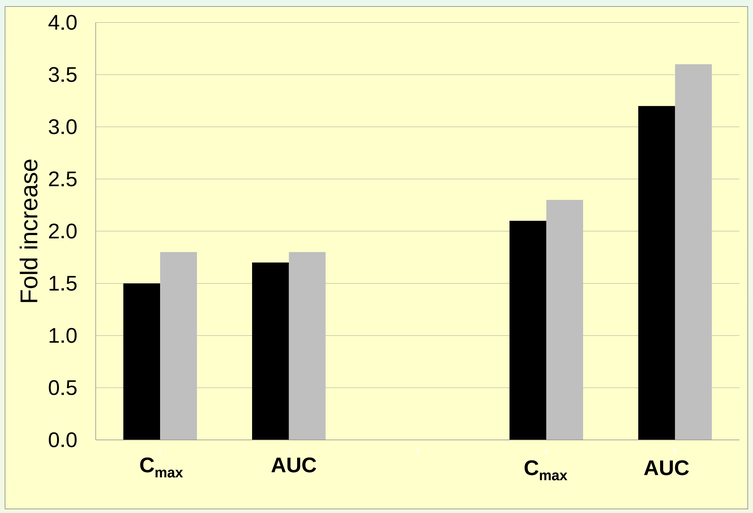

Figure 2. Predicted (black) and observed (grey) fold-increases in exposure (C_{max} and AUC) after a single 30 mg dose of paroxetine in subjects with differing degrees of RI (GFR < 30 ml/min/1.73 m^2 and 30-60 ml/min/1.73 m^2) relative to HV based on the study design described by Doyle *et al*. (1989).