Predicting Drug Interactions with Selective Serotonin Reuptake Inhibitors (SSRIs): Impact of Non-specific Binding and Active Uptake

A. Heydari*[1], K. Rowland-Yeo[2], M.S. Lennard[2], G.T. Tucker[1,2] and A. Rostami-Hodjegan[1,2]**

[1]Academic Unit of Clinical Pharmacology, University of Sheffield, UK ; [2]Simcyp Ltd, Blades Enterprise Centre, Sheffield, UK

*** Current Address: Faculty of Medicine, Urmia Medical and Health Science University, Urmia, Iran**

**** k.r.yeo@simcyp.com**

INTRODUCTION

- Long-term maintenance treatment of depression using selective serotonin re-uptake inhibitors (SSRIs) increases the possibility of co-prescription with other medications [1], and hence the potential for metabolic drug-drug interactions (mDDIs).
- Predicting the magnitude of *in vivo* mDDIs involving cytochrome P-450 enzymes from *in vitro* data requires accurate knowledge of the inhibition rate constants (competitive: Ki & mechanism-based: K_I) and an estimate of the inhibitor concentration ([I]) at the enzyme active site.

AIMS & OBJECTIVES

- To predict the magnitude of mDDIs observed in 86 clinical studies of 5 SSRIs (citalopram (CIT), paroxetine (PXT), sertraline (SER), fluoxetine (FXT), fluvoxamine (FVX)).
- To assess the influence of non-specific microsomal binding (NSMB) and active hepatic uptake (AU) on the overall performance of simulations and the accuracy of prediction.

METHODS

- Data were collated from published sources (*via* "WEB OF SCIENCE" (1981-2004) and "PUBMED" (1966-2004)) and our own unpublished data.
- *In vitro* Ki values were obtained from a meta-analysis of values weighted by the number of liver samples used in each study..
- For each SSRI, reported Ki values were plotted against the microsomal protein concentration used in the study (Figure 1) to obtain an unbiased Ki value at a protein concentration of zero.
- Ki values were also corrected by experimental fu_{mic} values from the literature or estimated values [2] to account for non-specific binding (NSMB).
- Mechanism-based inhibition of CYP2D6 and CYP3A4 was considered for by PXT and FXT, respectively.

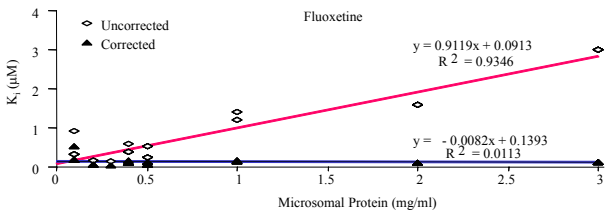

Figure 1. A representative graph showing K_i values for the inhibitory effect of FXT on *in vitro* CYP2D6 activity (varying substrates) as a function of microsomal protein concentration

MODELLING APPROACH

- The data were implemented in a physiologically-based pharmacokinetic model within Simcyp® software (version 5.0).
- The model accounted for time- and concentration-dependent inhibition or inactivation of active enzyme using unbound plasma drug concentration [I] as the driving force.
- The concentration gradient between unbound drug in hepatocytes and plasma (AU) was varied systematically from 1 to 30.

RESULTS & DISCUSSIONS

- The meta-analysis indicated that the SSRIs had the greatest inhibitory potency with respect to CYP2D6, with the exception of FV, a more potent inhibitor of CYP1A2 (K_i - 0.085 μM) The Ki values with respect to CYP2D6 are shown in Table 1.
- Despite using K_i values corrected for NSMB, the mDDIs with SSRIs were systematically under-predicted (Figure 2a).
- The magnitude of mDDIs caused by some, but not all SSRIs (e.g. FVX), could only be recovered when AU into hepatocytes was considered (Figure 2b).
- Failure to recover the extent of mDDIs with FVX may be explained by the fact that its metabolite (norfluoxetine) is also a potent inhibitor of CYP2D6.
- All mDDIs with the substrates desipramine and imipramine were substantially under-predicted. This may, in part, be due to the lack of enzyme kinetic data for several of the main metabolic routes of the two drugs.
- The contribution of a given metabolic pathway to the total clearance of a substrate (fm) has a major impact on the accuracy of prediction.

Table 1. Mean values (± SE) of K_i for SSRIs with respect to inhibition of CYP2D6 mediated metabolism

	n	K_i (μM)	K_iu (μM)[a]	K_iu (μM)[b]
CIT	8	45.3 (± 28.0)	3.4 (± 10.8)	5.4 (± 2.8)
FLX	12	1.2 (± 1.0)	0.099 (± 0.01)	0.14(± 0.02)
FVX	11	8.0 (± 5.8)	1.8 (± 0.3)	2.2 (± 0.4)
SET	10	23.4 (± 0.9)	3.1 (± 0.7)	0.57(± 0.11)
PXT	11	1.4 (± 1.1)	0.18 (± 0.02)	0.21 (± 0.02)

U – unbound; a – corrected using reported fu_{mic} values; b – corrected using calculated fu_{mic} values based on the Austin equation [2]

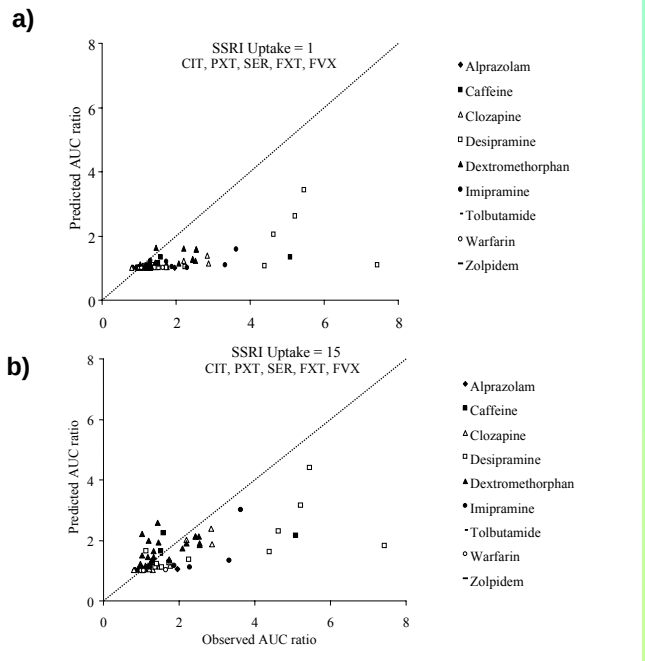

Figure 2. Predicted *versus* observed AUC ratios of a range of substrates in combination with SSRIs when AU is (a) ignored and (b) considered.

REFERENCES

1) Edwards, JG & Anderson, I (1999) *Drugs* **57**: 507-33.
2) Riley, R *et al.* (2002) *Drug Metab Dispos* **30**: 1497-1503.