Incorporation of Inter-Individual Variability into the Prediction of In Vivo Drug Clearance from In Vitro Data

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Introduction

Methods for predicting *in vivo* drug clearance from *in vitro* data were first described over 25 years ago (Rane *et al*. 1977). It is only more recently, with the increased availability of human liver samples, that such methods for *in vitro - in vivo* extrapolation (IVIVE) have been widely implemented (Iwatsubo *et al.* 1997; Obach *et al.* 1999). Virtually all of the reports on IVIVE have employed fixed (mean) parameter values to predict average clearances, and there has been relatively limited application of methods to assess the distribution of outcomes in populations.

The Simcyp Clearance and Interaction Simulator® software has been developed, in association with several major pharmaceutical companies, to simulate and predict drug clearance and metabolic drug-drug interactions in virtual populations using a Monte Carlo approach. It combines information on genetic, physiological, and demographic variability with preclinical *in vitro* data to allow extrapolation to *in vivo* pharmacokinetics. The aim of this study was to assess the ability of the software to predict the clearances of established drugs and the likely variability of their clearances.

Methods

Drug specific data were collated from the published literature after identifying sources using OVID MEDLINE (1966-2004) and WEB OF SCIENCE (1981-2004). The criteria for drug selection were that that their primary route of elimination was by cytochrome P450 (CYP) mediated metabolism, that they included recognised probes for specific CYPs or were metabolised mostly by a single isoform, that they covered a wide range of *in vivo* clearance values, and that they did not exhibit non-linear enzyme kinetics or substrate inhibition. Full studies providing values of V_{max} (pmol/min/pmol CYP) and K_m (µM) were the preferred source of metabolic data. Values obtained using microsomes prepared from recombinant systems expressing human CYPs (rCYPs) (lymphoblastoid, baculovirus, E.coli or yeast) were preferred as V_{max} values are reported directly per pmol P450. When derived using human liver microsomes (HLM), V_{max} values are expressed per mg protein, and conversion to rate per pmol CYP using CYP abundance data is required. It is well recognised that there are differences in turnover numbers between recombinant systems and HLM. Accordingly, intersystem extrapolation factors (ISEFs) (Proctor *et al.*, 2004), which reflect these differences in intrinsic activity per unit enzyme, were applied to *in vitro* metabolism data generated by rCYP systems. Median values specific to the expression system and each particular CYP were used. Values of fu_{mic} were obtained from published literature where available and adjusted for the microsomal protein content accordingly. All other fu_{mic} values were calculated according to the following equation (Austin *et al.*, 2002):

$$fu_{mic} = \frac{1}{C \cdot 10^{0.56\ \log P/D\ -1.41} + 1} \qquad (1)$$

The software (version 5.0) was used to predict total human plasma CL of 21 orally (*po*) and 14 intravenously (*iv*) administered drugs. The overall prediction accuracy of each drug was determined by comparing the median predicted CL with values obtained from *in vivo* healthy volunteer PK studies. The accuracy of predicting inter-individual variability for each drug was assessed by comparing the ratio of fold variability to median CL for both predicted and observed data (Equation 2).

$$\text{Variability Error} = \frac{CL(90\%CI)_{pre} / CL(median)_{pre}}{CL(90\%CI)_{obs} / CL(median)_{obs}} \qquad (2)$$

Results

A selection of low, medium and high clearance drugs were studied (Figure 1). The range of median observed *in vivo* CL_{po} values was 0.24 – 1529 L/h and CL_{iv} ranged from 0.25 – 54.9 L/h. For median clearance, 86% of CL_{po} and 100% of CL_{iv} predictions were within 2-fold of the observed values. For fold variability, 71% of both CL_{po} and CL_{iv} predictions were within 2-fold.

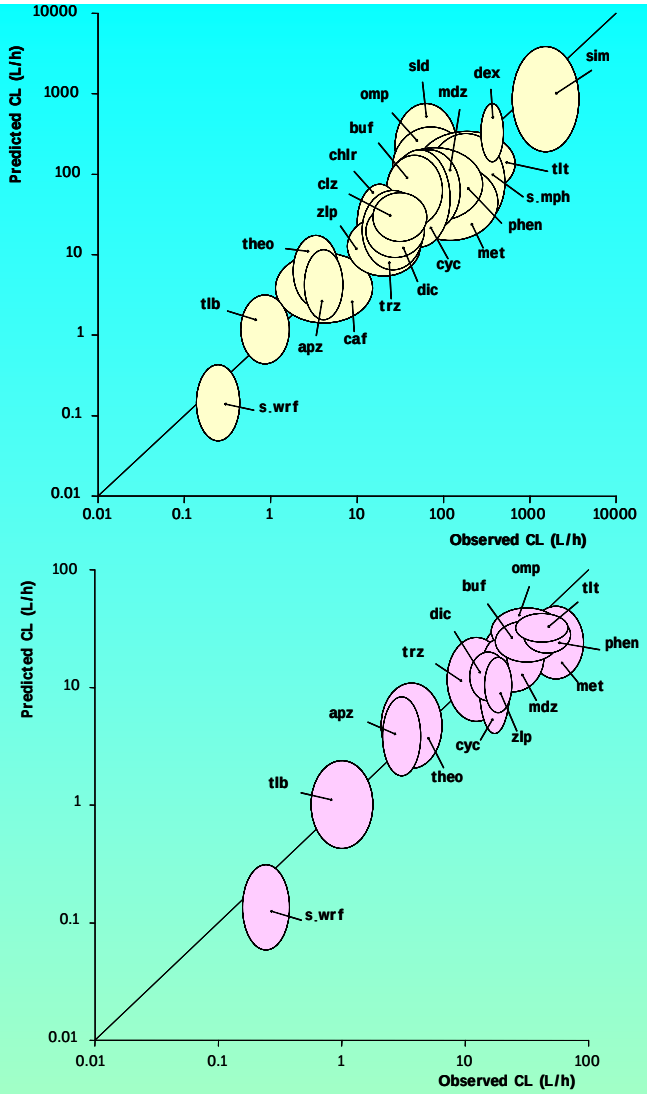

Figure 1: Predicted vs observed CL for 21 orally (top) and 14 intravenously (bottom) administered drugs. The ellipses represent the 90% confidence interval of both predicted & observed values. The line of identity is shown. Drug name key: apz = alprazolam, buf = bufuralol, caf = caffeine, chlr = chlorzoxazone, clz = clozapine, cyc = cyclosporine, dex = dextromethorphan, dic = diclofenac, met = metoprolol, mdz = midazolam, omp = omeprazole, phen = phenacetin, s-mph = s-mephenytoin, s-wrf = s-warfarin, sld = sildenafil, sim = simvastatin, theo = theophylline, tlb = tolbutamide, tlt = tolterodine, trz = triazolam, zlp = zolpidem

Discussion/Conclusions

- It appears that the use of *in vitro* metabolism data from rCYPs with applied ISEFs provide reasonable estimates of CL values.
- The importance of accounting for non-specific binding in microsomes, to ensure kinetic parameters are based on unbound concentrations of drug *in vitro*, has also been demonstrated. Underprediction of CL values is common especially for lipophilic bases such as tolterodine and dextromethorphan, where the extent of non-specific binding is high (fu_{mic} is low). Thus, fu_{mic} values are incorporated in all Simcyp predictions.
- Using the current data set, it appears that the software can predict median CL and the associated variability with reasonable confidence.

References

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References for all data available on request