Prediction of xenobiotic clearance in humans: *In vitro - in vivo* extrapolation (IVIVE) *vs* allometric scaling (AS)

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INTRODUCTION

Methods for predicting the clearance of xenobiotics in humans include:

(1) Interspecies *in vivo* allometric scaling (AS);
(2) Direct scaling from human *in vitro* data,
(3) Scaling from animal and human *in vitro* data combined with *in vivo* inter-species scaling [1].

The main drawback of AS is its empirical nature [2], although its utility is also affected by experimental design, the type, number and weight range of species used, and analytical error [3-4]. AS is often compromised by interspecies differences in metabolism [5], and can be criticised for ignoring interindividual variability, particularly that associated with human genetic polymorphisms related to cytochromes P450 [6]. Methods for predicting *in vivo* drug clearance from *in vitro* data were first described over 25 years ago [7], but they have not been utilised systematically until the last 13 years. This approach uses intrinsic clearance, obtained *in vitro* from human liver or recombinantly expressed CYP microsomes or hepatocytes, as part of a whole organ liver clearance model. The outcome is affected by many factors including the system used to obtain the *in vitro* data [8], the incubation conditions [9], the method used to obtain the enzyme kinetic data [10], the specific liver model used [11] and the effect of non-specific binding [12].

SIMCYP is a new tool for *in vitro – in vivo* extrapolation (IVIVE), which integrates human physiological, anatomical, genetic and epidemiological information with human *in vitro* data to predict the population distribution and likelihood of pharmacokinetic parameters. This approach differs from traditional techniques as it generates a range of values rather than point estimates, by incorporating variability in enzyme expression levels, age and renal function.

The objective of this study was to compare IVIVE using SIMCYP and AS methods for the prediction of the clearance of xenobiotics in humans.

METHODS

The literature was searched for drugs where adequate data were available on *in vitro* human metabolism and *in vivo* clearance in humans and other species. Prediction of human clearances by IVIVE was carried out using Simcyp® software. AS predictions were based on data from at least three animal species and used four different methods (when the data were not available for all three species, human data were included in the scaling), namely: (a) simple allometry (clearance = a × (body weight)^b) ; (b) correction for maximum life-span potential (CL×MLP); (c) correction for brain weight (CL×BrW); and (d) use of body surface area. Mahmood *et al.* (1996) proposed that correction factors should be applied selectively according to the value of the exponent of the simple allometric equation to improve the prediction of human drug clearance. This ''rule of exponents'' states that when $0.55 \leq b < 0.71$, no correction factor is necessary; when $0.71 \leq b < 1$, MLP should be incorporated into the scaling method; and when $b > 1$, BrW should be incorporated. The rule was applied (e) to all drugs in the present study. Prediction accuracy was described by mean fold error and the Pearson product moment correlation coefficient. Predictions were considered successful if the mean fold error was ≤ 2.

RESULTS

Data meeting the search criteria were available for 10 drugs given orally (alprazolam, caffeine, clozapine, cyclosporine, dextromethorphan, midazolam, omeprazole, sildenafil, tolbutamide, tolterodine) and 5 given intravenously (cyclosporine, diclofenac, midazolam, omeprazole, theophylline). Figure 1 shows the correlations between predicted and observed values of drug clearance found using each of the six methods. To assess the accuracy and bias of the predictions, the precision errors (expressed as the log of the predicted/observed CL ratio) were plotted as a function of predicted clearance (Figure 2), and various statistical parameters were calculated (Table 1). Incorporation of the empirical correction factors MLP and BrW, either universally or according to the rule of exponents, failed to improve the predictive performance of the AS method. Predictions were accurate (mean fold error range: 0.85 to 1.98) in 14/15 cases when IVIVE was used compared to 12, 11, 11, 9 and 10 cases using simple allometry, MLP, BrW, BSA, and the rule of exponents, respectively. The percentages of clearance predictions outside a 2-fold error are shown in Table 1.

Table 1. Statistical comparison of the accuracy of predictions using different methods.

	SIMCYP	Allometric scaling methods				
		BW	MLP	BrW	BSA	ER*
Mean Fold Error	1.54	2.10	2.82	3.85	2.50	2.51
Pearson correlation coefficient	0.97	0.88	0.88	0.85	0.83	0.80
% outside 2 fold error	7%	20%	27%	27%	40%	33%

BW; simple allometry, MLP; Maximum Life-span Potential (MLP) allometry, BrW; Brain Weight (BrW) allometry, BSA; Body Surface Area (BSA) allometry, *ER; allometric scaling using exponent rules.

CONCLUSIONS

The results of the present study demonstrate that none of the correction factors examined resulted in improvement in prediction by AS alone. Furthermore, none of the AS methods were as accurate as that based on IVIVE using SIMCYP.

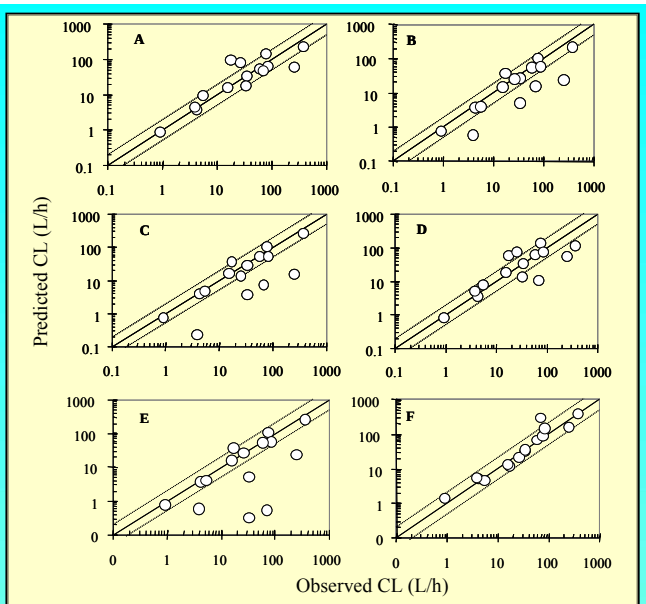

Figure 1. Relationship between the means of predicted and observed drug clearances. (A) Simple allometry, (B) Maximum Life-span Potential (MLP) allometry, (C) Brain Weight (BrW) allometry, (D) Body Surface Area (BSA) allometry, (E) Allometric scaling using exponent rules, and (F) *in vitro-in vivo* extrapolation using SIMCYP. The dashed and solid lines indicate 2-fold error and identity, respectively.

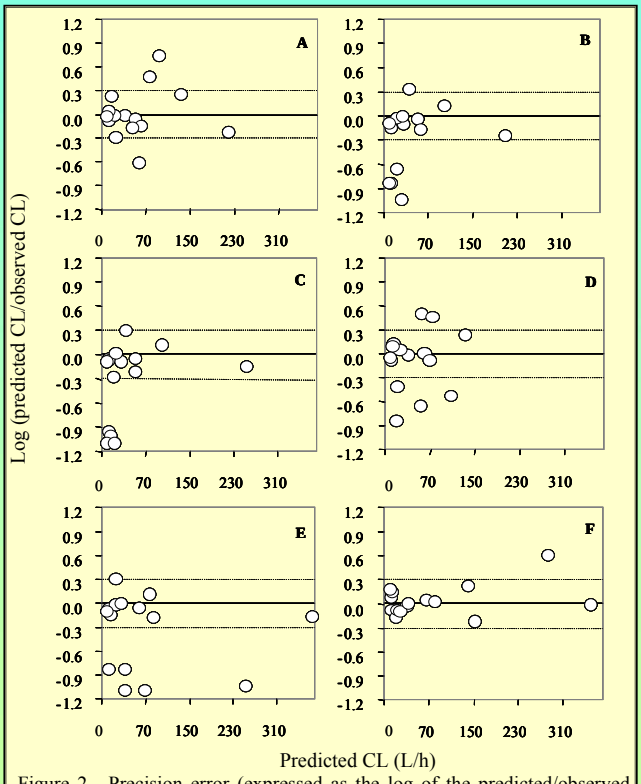

Figure 2. Precision error (expressed as the log of the predicted/observed CL ratio) for predicted CL values of 15 drugs determined using six different methods: (A) Simple allometry, (B) Maximum Life-span Potential (MLP) allometry, (C) Brain Weight (BrW) allometry, (D) Body Surface Area (BSA) allometry, (E) Allometric scaling using exponent rules, and (F) *in vitro - in vivo* extrapolation using SIMCYP. The dashed and solid lines indicate 2-fold error (± .3 log unit) in the predicted values and identity, respectively.

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