A comparison of single species allometric methods for the prediction of renal clearance in man

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Background

Success has been reported for some drugs when using allometric methods to predict renal clearance in man[1]. A toolbox for the allometric prediction of renal clearance using data from single or multiple species has been implemented in the Simcyp Simulator (V12.1). In comparison to conventional simple allometry which uses data from multiple species, predictions using direct correlation from a single animal species were recently shown by Paine *et al.* (2011) to perform well when predicting renal clearance for a database of 36 drugs, especially when correction factors for plasma protein binding and renal blood flow were taken into account[2]. However, there are several other single species allometric methods often used to predict total clearance that were not included in this analysis and may have an application in the prediction of renal clearance[3].

Aim

To expand the published database of renal clearance predictions and compare the utility of direct correlation methods to several other single species allometric methods for the prediction of renal clearance in man.

Methods

Via incorporation of data from several literature sources, the current database from Paine *et al*. 2011 was expanded to a total of 62 drugs with renal clearance and fraction unbound in plasma values in human, rat and dog.

Direct Correlation

Equation 1 was used for the prediction of human renal clearance from rat or dog data[2]. This method was tested with and without correction factors for fraction unbound in plasma (fu) and renal blood flow (Q_R). In cases where these were excluded, the corresponding terms were removed from Equation 1.

$$CL_{R\,h} = CL_{R\,sp} \cdot \left(\frac{BW_h}{BW_{sp}}\right) \cdot \left(\frac{fu_h}{fu_{sp}}\right) \cdot \left(\frac{Q_{R\,h}}{Q_{R\,sp}}\right) \qquad \text{Eq. 1}$$

Where CL_R and BW are renal clearance (in units of L/h) and body weight. Subscripts *h* and *sp* refer to values in human and animal species, respectively. Renal blood flow values in dog and rat were 1.95 $L.h^{-1}.kg^{-1}$ and 2.78 $L.h^{-1}.kg^{-1}$, respectively.

Power Function

Equation 2 was applied in a similar way to direct correlation (Equation 1) except with the inclusion of an exponent[3]. The standard allometric exponents of 3/4 and 2/3 were both investigated using this approach. In a similar way to the direct correlation method, this method was tested with and without correction factors for fu and Q_R.

$$CL_{R\,h} = CL_{R\,sp} \cdot \left(\frac{BW_h}{BW_{sp}}\right)^{exponent} \cdot \left(\frac{fu_h}{fu_{sp}}\right) \cdot \left(\frac{Q_{R\,h}}{Q_{R\,sp}}\right) \qquad \text{Eq. 2}$$

Coefficient Method

Equation 3 was applied, using species specific coefficient values which have been previously optimised to a dataset of total clearance values (n = 102)[4]. These were 0.41 for the dog and 0.152 for the rat.

$$CL_{R\,h} = CL_{R\,sp} \cdot coefficient_{sp} \cdot \left(\frac{BW_h}{BW_{sp}}\right) \qquad \text{Eq. 3}$$

Prediction success

Geometric mean fold-error (GMFE) and bias (GMFB) was assessed using Equation 4 and 5, respectively. In addition, the percentage of predicted renal clearance values within 2-fold of the observed values in man was used as a measure of prediction accuracy.

$$\text{Error} = 10^{\frac{1}{n}\cdot\sum\left|\log\left(\frac{Predicted}{Observed}\right)\right|} \qquad \text{Eq. 4}$$

$$\text{Bias} = 10^{\left|\frac{1}{n}\cdot\sum\log\left(\frac{Predicted}{Observed}\right)\right|} \qquad \text{Eq. 5}$$

Where a value close to 1 indicates a lower degree of prediction error or bias, respectively.

Results

- In line with Paine *et al.* 2011, predictions from dog data performed better than rat data in terms of both error and bias for all methods.
- From Figure 1, it can be seen that the power function and coefficient methods can perform better than direct correlation methods, especially in the absence of correction factors for plasma protein binding and renal blood flow.
- Incorporation of a correction factor for renal blood flow improved the prediction accuracy for the direct correlation method from rat data but reduced accuracy from dog data and dramatically reduced accuracy for both species using the power function method.

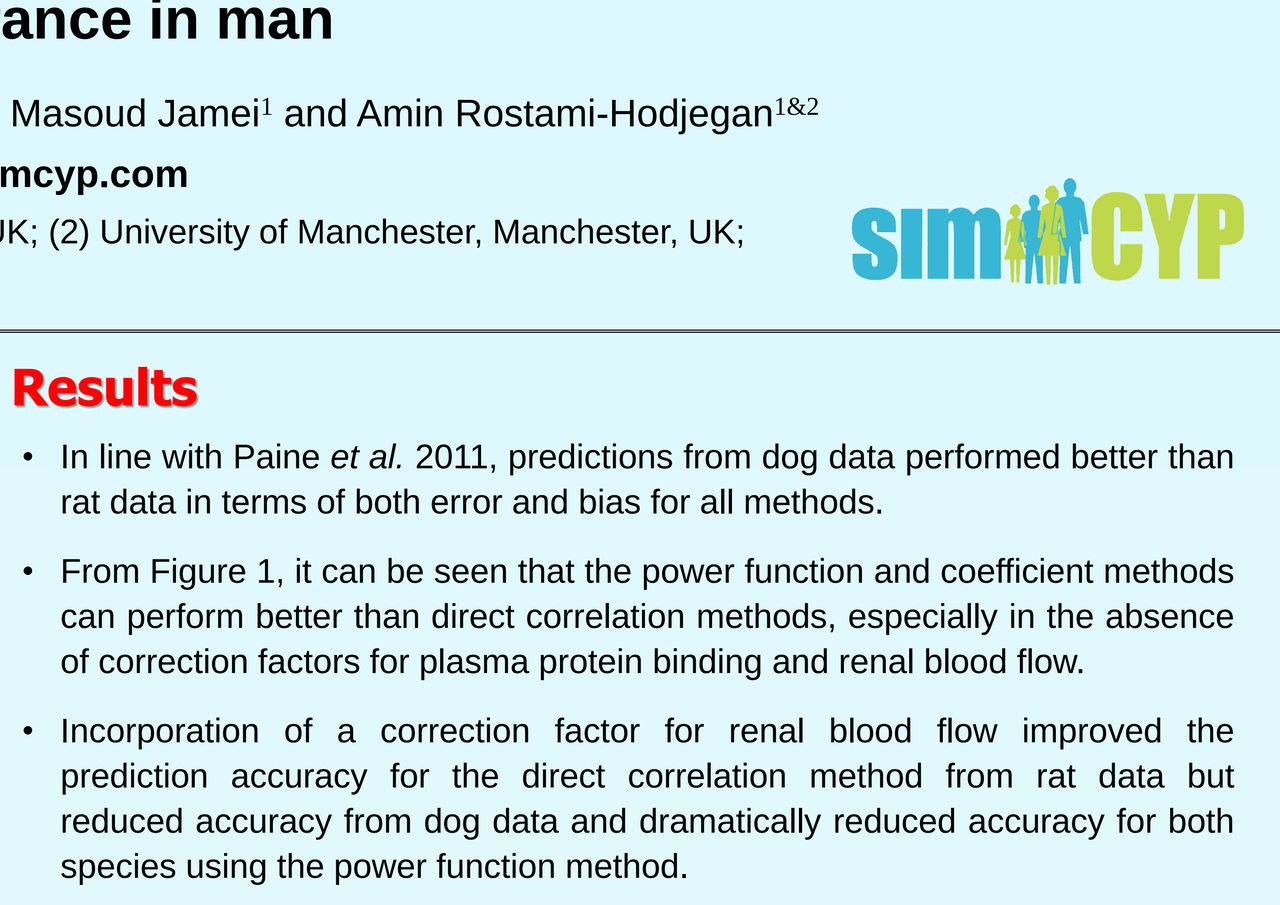

Figure 1. *A comparison of error and bias from single species methods for the allometric prediction of renal clearance from (A) dog (n=50) and (B) rat (n=60) data. The range of plot (A) is shown by the grey box on plot (B), indicating the extent of the difference between species.*

- For the coefficient method, optimisation of the coefficients to the current dataset did not lead to a significant improvement in prediction accuracy (data not shown).

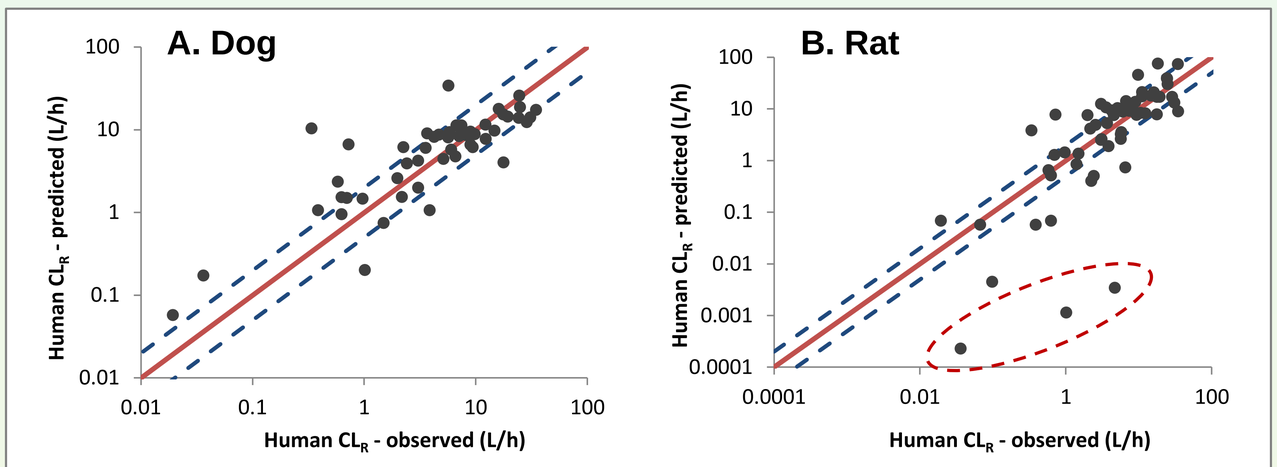

Figure 2. *A comparison of human observed against predicted renal clearance using the 3/4 power function approach from (A) dog and (B) rat data without any correction factors. Lines of unity and 2-fold either side are shown. The percentage within 2-fold was 64% and 57% for dog and rat, respectively. Outliers of the rat predictions which have been identified as possible OAT1 transporter substrates are indicted by the red circle.*

- Ibuprofen, losartan and indomethacin were outliers with significant under-prediction of human renal clearance from rat data (Figure 2). These acidic drugs are potent inhibitors and possible substrates of OAT1/3 uptake transporters on the basolateral membrane of proximal tubule cells. As these methods do not account for inter-individual variability in the expression of drug transporters they tend not to perform well for drugs that are extensively secreted into urine.

Conclusions

All single species methods tested have been shown to perform reasonably well under certain conditions. A limitation of this approach has been seen for several drugs that are likely to be actively secreted into urine by OATs. In these cases, the benefits of a mechanistic approach to the prediction of human renal clearance such as the MechKiM model in Simcyp would be even greater.

References:

1. Jezequel, SG. *et al*. (1994) *J Pharm Pharmacol* **46**: 196-199

2. Paine, SW. *et al.* (2011) *Drug Metab Dispos* **39**: 1008-1013

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4**.** Tang, H. *et al.* (2007) *Drug Metab Dispos* **35**: 1886-1893