A Novel Model for Prediction of Human Drug Clearance by Allometric Scaling

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Abbreviations: CL, clearance; Rfu, ratio of unbound fraction in plasma between rats and humans; ROE, rule of exponents;
Abstract

Sixty-one sets (61) of clearance (CL) values in animal species were allometrically scaled for predicting human clearance. Unbound fraction ($f_u$) of drug in plasma in rats and humans were obtained from the literature. A model was developed to predict human CL: $CL = 33.35 \text{ ml/min} \times (a/R_{fu})^{0.770}$, where $R_{fu}$ is the $f_u$ ratio between rats and humans and $a$ is the coefficient obtained from allometric scaling. The new model was compared with simple allometric scaling and the ‘rule of exponents’ (ROE). Results indicated that the new model provided better predictability for human values of CL than ROE. It is especially significant that for the first time the proposed model improves the prediction of CL for drugs illustrating large vertical allometry.
Introduction

Allometric scaling is widely used in predicting human clearance (CL) based on animal data. Since prediction errors are commonly observed in the practical application of this approach, various modifications to allometric scaling have been proposed. These modifications include: in vitro metabolic data (Lave, et al., 1997); correcting by either maximum life-span potential (MLP) or brain weight (BrW) (Mahmood and Balian, 1996b); the “rule of exponents” (ROE) (Mahmood and Balian, 1996a); scaling unbound CL (Feng, et al., 2000). Correction by in vitro metabolic data was successful in predicting human CL of ten extensively metabolized drugs (Lave, et al., 1997). Based on a data analysis of sixteen drugs, however, Mahmood concluded that the use of in vitro data obtained from liver microsomes to predict hepatic CL in humans did not provide reliable predictions (Mahmood, 2002). In addition, in vitro metabolic corrections cannot be applied to compounds eliminated by excretion. Scaling unbound CL across animal species improved the prediction for certain compounds (Feng, et al., 2000), however, it failed to predict well for a few compounds with large vertical allometry such as diazepam and valproate. Recently, Mahmood suggested that unbound CL cannot be predicted any better than total clearance (Mahmood, 2000). Corrections either with MLP or BrW have been shown to be inappropriate if they are used indiscriminately, which led to the idea of ROE. This rule provides selection criteria for use of MLP or BrW, based on the values of the exponents obtained from simple allometry (Mahmood and Balian, 1996a). Although ROE has been shown to improve the prediction significantly compared to simple
allometry, this method is still not satisfactory in predicting large vertical allometry. More recent studies (Nagilla and Ward, 2004) found that the corrections using MLP or BrW or the ‘rule of exponents’ in allometric scaling did not result in significant improvements in predictions of human CL. Furthermore, Ward et al. proposed that the monkey liver blood flow approach was superior to the ‘rule of exponents’. This controversy is currently not resolved (Mahmood, 2005; Nagilla and Ward, 2005).

The coefficients \((a)\) of the power function have been considered important in determining the magnitude of CL, because the exponents \((b)\) have been shown to be relatively constant with a typical value close to 0.75 (Boxenbaum, 1982). Based upon analysis of more than 60 drugs we have observed that the water-octanol partition coefficient (logP) and the ratio of unbound fraction (\(f_u\)) in plasma between rats and humans (Rfu) may provide simple rules for anticipating the occurrence of large vertical allometry. Based upon these findings, therefore, we attempted to develop a new model for predicting human CL.
Methods

A literature search was performed to obtain animal data for allometric scaling of systemic CL (CL used in this article refers to systemic CL) and $f_u$ ratio in rats and humans. Only data sets including at least three animal species were used for scaling. Coefficients and exponents were obtained by fitting: body weight and CL; CL×MLP; or CL×BrW on a log-log scale according to the allometric equation: CL or CL×MLP or CL×BrW = $a \times W^b$. CL in humans was calculated by using the coefficients and exponents obtained and human body weight reported or by assuming 70 Kg (if weight was not reported in the publication). MLP was calculated by using, 

$$\text{MLP} = 10.839 \times W^{0.636} \times BW^{-0.225}$$ (Boxenbaum, 1982). The rule of exponents was applied as described by Mahmood: 1) if the exponent from simple allometry is between 0.55 and 0.70, simple allometry is applied; 2) if the exponent is between 0.70 and 1.0, CL×MLP approach is applied; 3) if the exponent is greater than 1.0, CL×BrW approach is applied; 4) if the exponent is less than 0.50, simple allometry is applied since none of the approaches could improve the prediction (Mahmood and Balian, 1996a). Predictability was assessed by percentage error (PE), which is, 

$$\text{PE}_{\text{over}} = \frac{\text{CL}_{\text{pred}} - \text{CL}_{\text{obs}}}{\text{CL}_{\text{obs}}} \times 100\%$$, for over-prediction

and, 

$$\text{PE}_{\text{under}} = \frac{\text{CL}_{\text{obs}} - \text{CL}_{\text{pred}}}{\text{CL}_{\text{pred}}} \times 100\%$$, for under-prediction. A power model is proposed, 

$$\text{CL} = \alpha \prod_{i} p_i^{\beta_i} \quad (1)$$

and transformed into, 

$$\log \text{CL} = \log \alpha + \sum \beta_i \cdot \log P_i \quad (2)$$
where $P_i$ is the variable for $a$, $b$, $R_{fu}$ or $e^{\text{ClogP}}$ (exponential values of water-octanol partition coefficient, ClogP). The transformed model was screened by a backward step-wise procedure (P-value entrance criterion at 0.1 and P-value removal criteria at 0.2) to obtain parameters of statistical significance (Intercooled Stata 7.0, Stata, College Station, TX).
Results

The interest and rationale for developing a new allometric model equation was based on our previous findings that Rfu, combined with ClogP could be used to formulate rules to predict qualitatively the occurrence of large vertical allometry in predicting human CL (Tang and Mayersohn, Journal of Pharmaceutical Science, in press). The current study was undertaken to create and test a model in which parameters such as Rfu, ClogP, as well as coefficient \( a \) and exponent \( b \) from simple allometry, could potentially be useful to quantitatively predict human CL. ClogP was removed from the model since it did not add any statistical improvement. Coefficient \( a \), exponent \( b \) and Rfu were found to be statistically significant with P-values of < 0.001, <0.05, <0.001, respectively. The model equation incorporating these three variables was:

\[
CL = 36.6 \times \text{(ml/min)} \times a^{0.82} \times b^{0.71} \times Rfu^{-0.70} \quad (R^2 = 0.82)
\]  

(3)

The exponential value of \( b \) (0.71) is close to that of \( a \) (0.82) and Rfu (0.70). \( b \) is relatively constant and varies over a much narrower range (~ 0.35-1.20) than \( a \) (0.31-200) or Rfu (0.33-20), therefore, \( b \) was not considered to be an important variable. Thus, \( a \) and Rfu were used as the only variables to re-develop the model, which resulted in the simplified Equation 4,

\[
CL = 33.35(\text{ml/min}) \times a^{0.77} \times Rfu^{-0.71}
\]  

(4)

which retained an \( R^2 \) of 0.81, indicating that the three-variable model does not improve the prediction performance. Values for CL increase with \( a \), indicating that the coefficient \( a \) from simple allometry is a primary determinant of CL. In contrast, CL decreases when Rfu increases due to the negative power of Rfu. This inverse relationship makes sense in
that a higher value for fu in animals compared to humans may lead to an over-prediction of CL by simple allometry. The inverse functional relationship between fu and CL predicted in humans, therefore, may correct the over-predictions caused by significant differences in fu between animals and humans.

The exponents of a and Rfu have very similar absolute values. Changing -0.71 to -0.77 for the exponent of the fu ratio only slightly affects CL. For example, an Rfu of 10 raised to the power, -0.71 is 0.19; while 10 raised to the power, -0.77 is 0.17. Most fu ratios are smaller than 10, therefore, the equation was further simplified to,

$$CL = 33.35 (\text{ml/min}) \times \left(\frac{a}{Rfu}\right)^{0.77}$$ (5)

The term, $\frac{a}{Rfu}$, could be referred as an “fu–corrected-a”. The predictability of CL estimations for Equations 5, as well as for simple allometry and ROE, is given in Table 1. The significant improvement in prediction performance by the proposed model, compared to ROE, could be judged from three perspectives.

First, the average absolute value of percentage error by Equations 5, ROE and simple allometry were 78%, 185% and 323%, respectively. The significant improvement in prediction by the new model is apparent.

Second, using the new model (e.g., Equation 5), only six compounds had percentage errors over 200%, with 548% for diazepam and 200-300% for the other five. In contrast, 11 compounds using the ROE method had prediction percentage errors greater than 200%, with 2100% for GV150526A, 1626% for diazepam, 1485% for
tamsulosin, and 200-1000% for the other eight (Table 2). Therefore, the new model predicted the large vertical allometry with greater success compared to ROE.

Comparisons of the predictability of human CL from simple allometry with the new model (Equation 5) and ROE may be visualized in Figures 2 and 3. The dashed line in the graphs represents a 200% error range. Simple allometry results in substantial over-prediction of human CL for many compounds (especially those with low CL). The ROE method considerably reduces that error, while it still retains a few large over-predictions and leads to biased under-predictions. The under-predictions by the ROE method is primarily the result of applying MLP or BrW corrections to compounds having allometric exponents greater than 0.70. In contrast, the new model equation proposed here results in more accurate predictions of human CL and a more random pattern of errors.
Discussion

The use of $f_u$ ratio between rats and humans, rather than between all animals and humans, was based on our observation that the $f_u$ in rats is representative of the average $f_u$ in animals (Figure 1). In contrast, many significant differences between $f_u$ in rats and $f_u$ in humans were observed (Figure 1). One question could be raised concerning why scaling by the unbound CL approach did not provide stable and good predictability, because it appears that correcting CL by $f_u$ in each animal species would be more favorable than just considering only rats and humans. One possible explanation could be attributed to the serious error underlying data fitting to the power function (Smith, 1984) and the considerable measurement error of $f_u$, especially for highly plasma bound compounds.

When three or more animal species are included for scaling unbound CL, the same number of $f_u$ variables with errors are also introduced into the data fitting, and may generate greater error in predicting human values than what is generated from the error noted in only one species, the rat, in the new proposed model. Here is an example to visualize this concept. Suppose three species, mouse (0.03 kg), rat (0.25 kg) and dog (15 kg), are used for allometric scaling of unbound CL. The final predicted CL in humans by allometry can be expressed as:

$$CL_{predicted} = A \cdot (f_u_{mouse})^{0.36} \cdot (f_u_{rat})^{-0.17} \cdot (f_u_{dog})^{-1.19} \cdot (f_u_{human})^{1.0}$$

(6)

where $A$ is a function of CL observed in each animal species and the body weight of animals (derivation in Appendix). The new model can be expressed as:

$$CL_{predicted} = B \cdot (f_u_{rat})^{-0.77} \cdot (f_u_{human})^{0.77}$$

(7)
where $B$ is not equal to $A$, but is also a function of $CL$ observed in each animal species and the body weight of animals. It is obvious that the correction of $fu$ in each species incorporates more variance by introducing more $fu$ variables compared to both simple allometry and the new model.

Certainly, the new model is empirical just as are all of the other approaches. No solid physiological or biochemical basis could be offered at this time. The model proposed here does not consider many other potential types of useful information such as in vitro metabolic differences across species, which may account for deviations in predictions. Therefore, the empirical model that has been proposed should be expected, in practice, to result in errors in prediction, such as when a significant metabolic/elimination difference is seen across the species examined. Nevertheless, the new model was shown to be simple, reasonable, and more predictive than the currently available approaches. In particular, the new model significantly improves for the first time the prediction of the occurrence of large vertical allometry noted in humans.

In summary, a novel and simple model, incorporating $a$ and $fu$ ratio between rats and humans, has been proposed and shown to provide a better predictability than the currently available allometric techniques in estimating values of $CL$ in humans. Most important, it significantly improves the prediction of large vertical allometry.
Acknowledgement

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References


Footnotes

1. This work was presented at the American Association of Pharmaceutical Scientists Annual meeting, Salt Lake City, Utah, Oct. 26, 2003.

2. The proposed model (Equation 5) was tested using one example of large vertical allometry (reboxetine), whose data were available to the authors during the revision of the manuscript. We predicted an Rfu greater than 5 for reboxetine. The data kindly provided by one of the reviewers (courtesy of Pfizer, Inc.) showed fu values of 0.17 and 0.02 in rats and humans, respectively, which translate to an Rfu of 8.5. Prediction of human CL based upon Equation 5 resulted in a PE of 104%, compared to 1395% and 804% based upon simple allometry and ROE method, respectively.
Legends to Figures

**Figure 1:** Unbound fraction of drug in plasma ($f_u$) for the average in all animal species (top) and in humans (bottom) as a function of $f_u$ in rats for 61 compounds. The average $f_u$ values in animals are based on at least two animal species including rats. The solid lines indicate the lines of 5-fold or 0.2-fold. The dotted lines indicate the lines of 2-fold or 0.5-fold. The dashed lines indicate the lines of identity.

**Figure 2:** Predicted human clearance as function of observed human clearance. Predicted values are based upon simple allometry (top), the new model equation derived here (Equation 5; middle) and the ‘rule of exponents’ (bottom). The solid lines are the lines of identity and the dashed lines represent a range associated with 200% error.

**Figure 3:** Percentage error in prediction of human clearance as a function of observed human clearance. Percentage errors are from predictions based upon simple allometry (top), the new model Equation 5 (middle) and the ‘rule of exponents’ (bottom). The inset plots are limited to 400% error, which encompass most of the error range. The solid lines indicate 0% error. The dashed lines indicate the range associated with 200% error. Symbols: simple allometric slope values less than 0.7 (circle), 0.7-1.0 (triangle), greater than 1.0 (rectangle).
Table 1. Comparison of predictability of human clearance obtained from simple allometry, new model equations and ‘rule of exponents’. The order of drugs is arranged according to the ascending values of exponents obtained from simple allometry. PE: percentage error.

<table>
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<tr>
<th>Compounds</th>
<th>References</th>
<th>Rf\text{fu}</th>
<th>a</th>
<th>b</th>
<th>CL\text{obs} (ml/min)</th>
<th>CL\text{pred} (ml/min)</th>
<th>PE (CL\text{pred})</th>
<th>ROE (CL\text{pred})</th>
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<td>Indinavir</td>
<td>(Lin, et al., 1996)</td>
<td>1.15</td>
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<td>Felbamate</td>
<td>Midazolam</td>
<td>Dolasetron</td>
<td>Mibebradil</td>
<td>Quinidine</td>
</tr>
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<tr>
<td>FCE22101</td>
<td>(Efthymiopoulos, et al., 1991)</td>
<td>0.69</td>
<td>11.18</td>
<td>0.756</td>
<td>494</td>
<td>278</td>
<td>-79</td>
<td>285</td>
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<tr>
<td>NS-105</td>
<td>(Mukai, et al., 1999; Kumagai, et al., 1999)</td>
<td>1.00</td>
<td>7.90</td>
<td>0.759</td>
<td>141</td>
<td>199</td>
<td>41</td>
<td>164</td>
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<tr>
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<td>(Adusumalli, et al., 1991; Palmer and McTavish, 1993)</td>
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<td>1.50</td>
<td>0.766</td>
<td>30</td>
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<td>52.30</td>
<td>0.785</td>
<td>798</td>
<td>1465</td>
<td>84</td>
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<td>Dolasetron</td>
<td>(Sanwald-Ducray and Dow, 1997)</td>
<td>0.90</td>
<td>57.44</td>
<td>0.793</td>
<td>1232</td>
<td>1670</td>
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<td>818</td>
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<td>Mibebradil</td>
<td>(Lave, et al., 1997)</td>
<td>2.00</td>
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<td>0.804</td>
<td>532</td>
<td>2032</td>
<td>282</td>
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<td>Quinidine</td>
<td>Mahmood and Balian, 1996a; Chiou and Hsu, 1988</td>
<td>1.41</td>
<td>47.51</td>
<td>0.805</td>
<td>330</td>
<td>1452</td>
<td>340</td>
<td>500</td>
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<td>Sumatriptan</td>
<td>(Cosson, et al., 1997)</td>
<td>1.01</td>
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<td>0.808</td>
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<td>Izumi, et al., 1997; Izumi, et al., 1996</td>
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<td>0.810</td>
<td>411</td>
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<td>0</td>
<td>236</td>
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<td>Theophylline</td>
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<td>0.69</td>
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<td>51</td>
<td>61</td>
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<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
<td>Value 5</td>
<td>Value 6</td>
<td>Value 7</td>
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<td>Amlodipine</td>
<td>(Stopher, et al., 1988)</td>
<td>3.00</td>
<td>29.00</td>
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<td>949</td>
<td>94</td>
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<td>DA-1131</td>
<td>(Kim, et al., 1998a; Kim, et al., 1998b)</td>
<td>1.00</td>
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<td>0.825</td>
<td>353</td>
<td>385</td>
<td>9</td>
<td>220</td>
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<td>Alfentanil</td>
<td>(Bjorkman and Redke, 2000)</td>
<td>1.23</td>
<td>24.85</td>
<td>0.834</td>
<td>448</td>
<td>859</td>
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<td>Norfloxacin</td>
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<td>90.02</td>
<td>0.836</td>
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<td>3139</td>
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<td>0.855</td>
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<td>13</td>
<td>13</td>
<td>22</td>
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<td>Methohexitone</td>
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<td>1000</td>
<td>2777</td>
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<td>999</td>
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<td>0.870</td>
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<td>(Hutchaleelaha, et al., 1997; Robbie and Chiou, 1998)</td>
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<td>1.03</td>
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<td>19</td>
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<td>Fentanyl</td>
<td>(Bjorkman and Redke, 2000)</td>
<td>1.06</td>
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<td>730</td>
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<td>3117</td>
<td>182</td>
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<td>SU 5416</td>
<td>(Sukbuntheng, et al., 2001)</td>
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<td>2652</td>
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<td>Ciprofloxacin</td>
<td>(Mahmood, 1999; Siefert, et al., 1986)</td>
<td>1.10</td>
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<td>0.927</td>
<td>423</td>
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<td>7.04</td>
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<td>(Reference)</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>F</td>
<td>G</td>
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<tr>
<td>ACNU</td>
<td>(Mitsuhashi, et al., 1990)</td>
<td>1.87</td>
<td>50.71</td>
<td>0.957</td>
<td>805</td>
<td>2950</td>
<td>266</td>
<td>423</td>
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<td>Ethosuximide</td>
<td>(Mahmood and Balian, 1996a;</td>
<td>1.00</td>
<td>0.60</td>
<td>1.012</td>
<td>13</td>
<td>44</td>
<td>240</td>
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<td></td>
<td>Battino, et al., 1995)</td>
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<tr>
<td>Thiopentone</td>
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<td>330</td>
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<td></td>
<td>(Park, et al., 1988;)</td>
<td></td>
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<td>Warfarin</td>
<td>(von Oettingen, et al., 1975;</td>
<td>15.00</td>
<td>0.37</td>
<td>1.126</td>
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<td>44</td>
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<td></td>
<td>Nagashima and Levy, 1969)</td>
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<td>Ro25-6833</td>
<td>(Richter, et al., 1998)</td>
<td>0.58</td>
<td>1.10</td>
<td>1.180</td>
<td>27</td>
<td>165</td>
<td>513</td>
<td>55</td>
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<td>GV150526A</td>
<td>(Iavarone, et al., 1999)</td>
<td>13.50</td>
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<td>1.196</td>
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<td>322</td>
<td>5266</td>
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<td>STDEV</td>
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<td>185</td>
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**Table 2:** A summary of outliers for predictions of human clearance (PEs greater than 200%) based on simple allometry, new model equation and ‘rule of exponents’. PE: percentage error. APE: average of absolute percentage error.

<table>
<thead>
<tr>
<th>Methods</th>
<th>APE</th>
<th>N (PE &gt; 200%)</th>
<th>N (PE &gt; 500%)</th>
<th>N (PE &gt;1000%)</th>
</tr>
</thead>
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<tr>
<td>Simple allometry</td>
<td>323%</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Rule of exponents</td>
<td>185%</td>
<td>11</td>
<td>6</td>
<td>3</td>
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<tr>
<td>Equation 5</td>
<td>78%</td>
<td>6</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>
Appendix: Derivation of Equation 5

Part I: Derivation of the function relating predicted PK parameters in humans (\(P_{\text{predicted}}\)) to animal body weights (\(W\)) and observed animal PK parameters (\(P_i\)).

The log-log transformation of, \(P = a \cdot W^b\) gives,

\[
\log P = \log a + b \cdot \log W
\]  

Let

\[
Y = \log P; \quad X = \log W; \quad a = 10^\alpha; \quad b = \beta
\]

Then, Equation (1) can be simplified to,

\[
Y = \alpha + \beta \cdot X
\]  

Suppose \(n\) different animal species are used for allometric scaling. Therefore, there are \(n\) sets of \((X, Y)\) data to fit using linear regression. Based on the method of least squares for linear regression, \(\alpha\) and \(\beta\) can be calculated as,

\[
\beta = \frac{\sum_{i=1}^{n} (X_i - \overline{X})(Y_i - \overline{Y})}{\sum_{i=1}^{n} (X_i - \overline{X})^2}
\]  

\[
\alpha = \overline{Y} - \beta \cdot \overline{X}
\]

Substituting, \(Y = \log P; \quad X = \log W\) into Equation A-3 and A-4, and further substituting \(\alpha\) and \(\beta\) into \(a = 10^\alpha; \quad b = \beta\), expressions of \(a\) and \(b\) are obtained as,

\[
a = \prod_{i=1}^{n} P_i^{A_i}
\]
\[
b = \sum_{i=1}^{n} B_i \cdot \log P_i \quad \text{A-6}
\]

where,

\[
A_i = \frac{1}{n} (1 - B_i \cdot \log \prod_{j=1}^{n} W_j) \quad \text{A-7}
\]

\[
B_i = \frac{1}{n} \cdot \frac{\log \frac{W_i^{n-1}}{\prod_{k=1}^{n} W_k}}{\sum_{k=1}^{n} (\log W_k - \frac{\log \prod_{i=1}^{n} W_i}{n})^2} \quad \text{A-8}
\]

By assuming a human body weight of 70 Kg, the predicted \( P \) in humans is obtained from,

\[
P_{\text{predicted}} = a \cdot 70^b = \prod_{i=1}^{n} P_i^{(A_i + 1.845B_i)} \quad \text{A-9}
\]

where \( P_{\text{predicted}} \) is the predicted PK parameter in humans, \( P_i \) is the measured PK parameter in an animal species,

\[
A_i = \frac{1}{n} (1 - B_i \cdot \log \prod_{j=1}^{n} W_j) \quad \text{A-10}
\]

\[
B_i = \frac{1}{n} \cdot \frac{\log \frac{W_i^{n-1}}{\prod_{k=1}^{n} W_k}}{\sum_{k=1}^{n} (\log W_k - \frac{\log \prod_{i=1}^{n} W_i}{n})^2} \quad \text{A-11}
\]
where \( W \) is the animal body.

**Part II: Derivation of Equation 5 based on Equation A-9**

Based on Equation A-9, predicted human CL (\( \text{CL}_{\text{predicted}} \)) using simple allometry from a combination of animals such as the mouse (0.03 kg), rat (0.25 kg) and dog (15 kg) gives,

\[
\text{CL}_{\text{predicted}} = (\text{CL}_{\text{mouse}})^{0.36} \cdot (\text{CL}_{\text{rat}})^{0.17} \cdot (\text{CL}_{\text{dog}})^{1.19}
\]  

A-11

Since,

\[
\text{CL}_u = \frac{\text{CL}}{f_u}
\]  

A-12

scaling of unbound CL can be done by substituting \( \text{CL}_u \) for \( \text{CL} \), resulting in,

\[
(\frac{\text{CL}_{\text{predicted}}}{f_u})^{1.0} = (\frac{\text{CL}_{\text{mouse}}}{f_u})^{0.36} \cdot (\frac{\text{CL}_{\text{rat}}}{f_u})^{0.17} \cdot (\frac{\text{CL}_{\text{dog}}}{f_u})^{1.19}
\]  

A-13

Therefore, CL predicted in humans by scaling unbound CL can be obtained,

\[
\text{CL}_{\text{predicted}} = A \cdot (f_u_{\text{mouse}})^{0.36} \cdot (f_u_{\text{rat}})^{-0.17} \cdot (f_u_{\text{dog}})^{-1.19} \cdot (f_u_{\text{human}})^{1.0}
\]  

A-14

where \( A \) is the CL value predicted in humans using simple allometry and is equal to,

\[
A = (\text{CL}_{\text{mouse}})^{-0.36} \cdot (\text{CL}_{\text{rat}})^{0.17} \cdot (\text{CL}_{\text{dog}})^{1.19}
\]  

A-15

By substituting \( a \) from Equation A-5, the new model equation (Equation 5 in text), is

\[
\text{CL} = 33.35(\text{ml} / \text{min}) \cdot (\frac{a}{Rf_u})^{0.77}
\]  

A-16

can be expressed as,
That is,

\[ \text{CL}_{\text{predicted}} = B \cdot (f_u^{\text{rat}})^{-0.77} \cdot (f_u^{\text{human}})^{0.77} \]  

where,

\[ B = 33.35(\text{ml/min}) \cdot (\prod_{i=1}^{n} P_i^{\lambda_i})^{0.77} \]
Fig 2

Simple allometry

Equation 5

Rule of exponents
Fig 3

Simple allometry

Equation 5

Rule of exponents