Prediction of human renal clearance from preclinical species for a diverse set of drugs that exhibit both active secretion and net re-absorption

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Running title: Prediction of human renal clearance

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Abbreviations: ADME, absorption, distribution, metabolism and excretion; afe, average fold error; CLr, renal clearance; CLp, plasmatic clearance; fu, unbound plasma fraction; GFR, glomerular filtration rate; KBF, kidney blood flow; NSAID, non-steroidal anti-inflammatory drug; OAT, organic anion transporter; OATP, organic anion transport protein; PPB, plasma protein binding; rmse, root mean square error.
Abstract

Identifying any extra-hepatic excretion phenomenon in preclinical species is crucial for an accurate prediction of the pharmacokinetics in man. This is particularly the case for drugs with a small volume of distribution, as they require an especially low total clearance in order to be suitable for a once-a-day dosing regimen in man. In this study, three animal scaling techniques were applied for the prediction of the human renal clearance of 36 diverse drugs that show active secretion or net re-absorption: (1) direct correlations between renal clearance in man and each of the two main preclinical species (rat and dog), (2) simple allometry and (3) Mahmood’s renal clearance scaling method. The results show clearly that the predictions to man for the methods are improved significantly when corrections are made for species differences in plasma protein binding. Overall, the most accurate predictions were obtained by using a direct correlation with the dog renal clearance after correcting for differences in plasma protein binding and kidney blood flow ($R^2 = 0.84$), where predictions on average were within 2 fold of the observed renal clearance values in human.
Introduction

In the last 10 years the pharmaceutical industry has become a very competitive area facing new challenges. Costs of discovering and developing a new chemical entity have quadrupled since 1987, mainly due to attrition during the development process (DiMasi et al., 2003). While reasons for attrition are varied, including portfolio decisions and lack of clinical efficacy of the biological mechanism, many reasons for compound failure are still related to unfavourable absorption, distribution, metabolism and excretion (ADME) properties of new drug candidates. This has generated intense efforts to identify potential ADME challenges with significant intellectual and financial investment in optimising pharmacokinetic parameters of molecules at the earliest stages of discovery, prior to any costly clinical trials.

The concept of body clearance not only includes metabolic clearance (hepatic or extra-hepatic) but also the excretion of unchanged drug in the bile or the urine. Therefore identifying and understanding any extra-hepatic excretion phenomenon in preclinical species is crucial for an accurate prediction of the pharmacokinetics in man. This is particularly the case for drugs with a low volume of distribution, as they require an especially low total clearance in order to be suitable for a once-a-day dosing regimen in man. As a consequence, the probability of encountering renal clearance in man and the impact it would have on the half-life requires investigation at an early stage in the discovery process.

Renal clearance of xenobiotics involves several major processes, i.e. passive glomerular filtration, active tubular secretion, passive and active re-absorption. Due to the complexity of this phenomenon, various animal scaling approaches have been
used in this study for the prediction of renal clearance in man for a diverse set of 34 marketed and 2 experimental drugs (Beaumont et al., 2000, Webster et al., 2003). The most basic animal scaling technique consists in using pharmacokinetics parameters obtained in preclinical species as a prediction for human (Boxenbaum, 1982). Furthermore, simple allometry scaling uses the combination of values measured in several preclinical species to predict man (Boxenbaum, 1980). This approach, based on body weight, has been used to predict total clearance in man (Kaye et al., 1997). This scaling method is based on the following function:

\[ Y = aW^b \]

Where \( Y \) is clearance, \( W \) is body weight, \( a \) and \( b \) are the coefficient and exponent of the allometric equation, respectively. However, pharmacokinetic parameters cannot always be accurately predicted using this approach and several modified methods have been suggested over the years.

Mahmood published a study in which he adapted simple allometry to predict the renal clearance of 10 actively secreted drugs (Mahmood, 1998). To that end, a normalising factor was applied to the renal clearance of species that exhibit active renal secretion. This factor took into account glomerular filtration rate (GFR), kidney blood flow (KBF), body weight and kidney weight. Despite the various studies published on the use of allometric scaling for the prediction of clearance, surprisingly very little is known about the ability of this technique to predict accurately the renal clearance of a diverse set of drugs (acids, bases, neutrals and zwitterions) that exhibit both active secretion and net re-absorption. The aim of this study was to use measurements of renal clearance in the two most common preclinical species (rat and dog) and
Materials and methods

The renal clearance data for a diverse set of 36 drugs in rat, dog and human were obtained from the literature or measured in-house. Plasma free fraction in the three species was also obtained for the set of 36 drugs and was used in conjunction with the renal clearance measurements for scaling purposes. Where no data were available in the literature, plasma protein binding was measured in-house.

Chemicals All compounds were obtained from Sigma-Aldrich (Poole, UK) with the exception of ramatroban and ampicillin, which were synthesised at AstraZeneca. Sodium bicarbonate, ethanol and phosphoric acid were obtained from Fisher Scientific (Loughborough, UK). Methanol was purchased from Romia (Cambridge, UK). Formic acid was obtained from VWR International (Poole, UK).

Pharmacokinetics studies

All in vivo work was subject to internal ethical review and conducted in accordance with Home Office requirements under the Animals Scientific Procedures Act (1986).

Bile-duct cannulated rats Male rats were obtained from Charles River (Margate, UK). They were housed in a light-controlled room, kept at a temperature of 18°C ± 2°C, and a level of 55% ± 10% humidity. They received a RM3 diet (Special Diet Services, UK) and had access to water ad libitum. After at least 1 week of acclimatisation, rats (250-350g) were surgically prepared under isoflurane anaesthesia. The bile duct was cannulated and cannulae were also implanted into the jugular vein (dosing cannula) and carotid artery (blood sampling cannula). Dose
solutions were administered via the intravenous (jugular vein) cannula as a bolus dose of 1 mg/kg. Serial plasma samples (200 - 300 uL) were taken from the intra-arterial (carotid artery) cannula. Approximately 200 μL of blood was drawn through the cannula prior to taking a sampling aliquot to ensure circulating blood was sampled through the cannula. Blood samples were taken over the time-course 2, 4, 8, 15, 30, 60, 120, 180, 240, 300, 360, 420 mins. Bile was collected over 7 hours. Rats were kept in metabolism cages over 7 hours for urine collection onto dry-ice.

**Bile-duct cannulated dogs** Male beagle dogs were obtained from Harlan (Bicester, UK). They were housed in a light-controlled room, kept at a temperature of 18°C ± 2°C, and a level of 55% ± 10% humidity. They received a Teklad 2021 diet (Harlan) and had access to water ad libitum. After at least 4 weeks of acclimatisation, a chronic bile duct cannulation was performed on two dogs following the technique described by Kissinger and Garver (1998). Dogs were allowed to recover from surgery for a minimum of one month.

The dose (1 mg/kg) was administered to the dogs (n=2) via a 30-minute infusion in the cephalic vein. Approximately 2.5 mL of blood was collected on EDTA via the jugular vein 0, 15, 30, 60, 120, 180, 300, 420, 720 and 1440 minutes after the beginning of the infusion. Bile was collected over 24 hours. Dogs were kept in metabolism cages over 24 hours for urine collection onto dry-ice.

**Sample analysis** Plasma, bile and urine samples were prepared within 30 minutes of collection according to the following procedure. Blood was centrifuged at 1110 x g for 10 minutes at 4°C. Plasma was transferred into plain polypropylene tubes, each prepared in advance to contain 1.5 μL of concentrated phosphoric acid to stabilize any
potential acyl glucuronide metabolites. Samples were then immediately frozen upright on dry ice and stored at -20°C. Bile and urine samples were treated with phosphoric acid, frozen and stored as previously described for plasma.

Concentrations of drugs were determined by a HPLC-mass spectroscopy method. Compounds were extracted from their biological matrix (50 µL) after addition of methanol containing an internal standard (150 µL). Samples were frozen for at least one hour at -20°C to precipitate the proteins. They were then centrifuged at 2050 × g for 20 minutes at 4°C. 10 µL of supernatant was injected into the mass spectrometer.

The mobile phases were water and methanol, both containing 0.1% formic acid (v/v). The column was a Waters Symmetry C8 3.5 µm (2.1 x 30 mm). Detection used a Quattro Ultima (Micromass, Waters, Milford, MA, USA) in negative electrospray ionization mode with data analysis on Quanlynx software (v. 4.0, Micromass).

**Pharmacokinetic analysis**  Pharmacokinetic parameters were calculated using WinNonlin (v. 3.2, Pharsight Corporation, Mountain View, CA, USA). Plasma clearance (CLp) was determined from the dose and plasma AUC\(_{0-\infty}\) with less than 20% extrapolation in all cases. Renal clearance was calculated using the following equation:

\[
CL_r = CL_p \times \% \text{ dose unchanged in urine} \tag{1}
\]

where CLr and CLp are the renal and total clearances, respectively, expressed in mL/min/kg.
Plasma protein binding determination

Where no data was available in the literature, plasma protein binding (PPB) was measured in human, dog and rat following the method described by Fessey et al. (2006).

Animal scaling

Renal clearance in man was predicted using the following three allometric approaches. Scaling was performed with both unbound and bound renal clearance in order to assess the influence of differences in plasma protein binding.

Method I: Direct correlations

Renal clearance values in man were estimated from the rat or dog renal values. Renal clearances were predicted directly from the preclinical species using the following simple equation:

$$CL_{r_{Human}} = CL_{r_{Species}}$$  \hspace{1cm} (2)

 Corrections for PPB differences were calculated using the following equation:

$$CL_{r_{Human}} = CL_{r_{Species}} \times \frac{fu_{Human}}{fu_{Species}}$$  \hspace{1cm} (3)

Further corrections for kidney blood flow differences were calculated as follows:

$$CL_{r_{Human}} = CL_{r_{Species}} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$  \hspace{1cm} (4)

Where $CL_{r_{Human}}$ and $CL_{r_{Species}}$ and $fu_{Human}$ and $fu_{Species}$ and $KBF_{Human}$ and $KBF_{Species}$ are the renal clearance, fraction unbound in plasma and kidney blood flows in man and rat or dog, respectively.
Method II: Simple allometry  The following allometric equation was used to predict renal clearance in man:

\[ CLr = a(W)^b \]  (5)

Where \( CLr \) is renal clearance, \( W \) is body weight and \( a \) and \( b \) are the coefficient and exponent of the allometric equation, respectively. When correcting for PPB, unbound renal clearance in human was predicted from unbound renal clearance in rat and dog using Equation 5. Predicted total renal clearance values were then estimated using the following equation:

\[ CLr_{\text{Predicted total}} = CLr_{\text{Predicted unbound}} \times fu_{\text{Human}} \]  (6)

Method III: Mahmood’s renal clearance scaling method  Mahmood’s method to predict renal clearance is based on the simple allometry method, but takes into account the kidney physiological differences between human and preclinical species. First a Species Specific Factor (SSF) is calculated for every species (7). This coefficient is then divided by the value obtained for human to produce a correction factor (8).

\[ SSF = \frac{(\text{Glomerular filtration} \times \text{Kidney blood flow})}{(\text{Body weight} \times \text{Kidney weight})} \]  (7)

\[ \text{Correction factor} = \frac{SSF_{\text{Species}}}{SSF_{\text{Human}}} \]  (8)
Values used for rat, dog and human kidney blood flow (KBF) were 52 (Hsu et al, 1975), 22 (Keil et al, 1989) and 16 ml/min/kg (Wolf et al, 1993), respectively. GFR values used for rat, dog and human were 5.2, 3.2 and 1.8 ml/min/kg (Mahmood, 1998), respectively. Renal clearance values of all the species that exhibit active secretion (CLr > GFR x fu) are normalised using the above correction factor and then used in a simple allometry equation (5). When using unbound clearances, predicted values were treated as previously described (6).

Statistics

The accuracy of prediction was compared between the 3 different methods. Precision of each approach was estimated by measuring the root mean squared error (rmse) and the average fold error (afe), respectively.

\[
\text{mse} = \frac{1}{N} \sum (\log \text{Predicted} - \log \text{Observed})^2
\]  

\[
\text{rmse} = \sqrt{\text{mse}}
\]

\[
\text{afe} = 10^{\text{mse}}
\]

The bias of each method was expressed as follows:

\[
\text{Bias} = 10^{\frac{1}{N} \sum \log \left| \frac{\text{Predicted}}{\text{Observed}} \right|}
\]

This parameter explains how the data are related to the line of unity. A bias greater than 1 means that the method over-predicts the observed results. However, if the bias tends to 0, then the method under-predicts the actual results.
Results

Human, dog and rat renal clearance and plasma free fraction values for the 34 marketed and 2 experimental drugs are shown in Table 1. Data from this table with references can be found in (supplemental Table 1). Figure 1 shows that 22, 20 and 26 out of the 36 drugs have unbound renal clearance values greater than GFR for human, dog and rat, respectively. Therefore, the 36 drugs represent chemistries of different charge type and exhibit examples of active secretion and net re-absorption.

The predictions from the different scaling methods versus the measured human renal clearance values are represented graphically in Figures 2 and 3 and the statistical analysis of these predictions are summarised in Table 2. Rat and human renal clearances are weakly correlated with one another, $R^2 = 0.52$ (Figure 2a, Table 2). Human renal clearance covers 3 orders of magnitude versus 5 for rat leading to a flat relationship. Moreover, the high/low clearance compounds in rat tend to be several fold higher/lower than their corresponding human values, respectively. The overall bias of the human versus rat correlation is 2.5 suggesting that on average rat has higher renal clearance than human (Table 2). Correcting for differences in PPB slightly tightens the correlation ($R^2 = 0.56$), however, several organic anions still appear to be under-predicted in man using the adjusted rat renal clearance (Figure 2c). While some improvement is afforded by adjusting rat renal clearance for PPB differences an overall bias still exists. Adjusting rat renal clearance for both PPB and KBF differences reduces the bias down to 1.4 (Figure 2e, Table 2). The majority of the human and rat data now lie along a line of unity, however, the organic anions; ibuprofen, indomethacin, losartan and ramatroban remain outliers. Therefore, using
this method would predict human renal clearance well for a diverse set of drugs but may also under-predict certain organic anions. Dog and human renal clearances are also weakly correlated, $R^2 = 0.51$ (Figure 2b, Table 2). The overall bias of the human versus dog correlation is 2.3 suggesting that on average dog has higher renal clearance than human (Table 2). Correcting for differences in PPB dramatically tightens up the correlation ($R^2 = 0.84$) and bias is reduced to 1.3 (Figure 2d). The aforementioned organic anions are no longer outliers and bias is further reduced to 1.1 by adjusting dog renal clearance for both PPB and KBF differences (Figure 2f, Table 2). The human and adjusted dog data now lie along a line of unity with an afe of 2.2 suggesting that this method predicts human renal clearance very well for a diverse set of drugs.

Applying simple allometry to the rat and dog renal clearance data in order to predict man does not improve the accuracy of the results. The average fold errors obtained with the simple allometry technique are 4.9 and 3.4 when using bound and unbound data, respectively (Figures 3a & 3b, Table 2). However, there is no bias in the predicted human renal clearance from unbound allometry when compared to the observed values. Finally, Mahmood’s method offers a slight improvement over simple allometry with average fold errors of 4.1 and 3.2 when using bound and unbound data, respectively (Figures 3c & 3d, Table 2). The two allometry methods show weaker statistics compared to predicting human renal clearance from dog renal clearance after adjusting for PPB and KBF differences.
Discussion

This study highlights the important influence that plasma protein binding has on active secretion as well as passive renal clearance processes in rat, dog and human. It is generally accepted that only unbound drug is subject to glomerular filtration, however, there is less agreement on the influence of plasma protein binding on active secretion. Bow et al. (2006) recently demonstrated that the in vitro uptake of the acid molecule Ochratoxin A by OATs 1, 3 and 4 and OATPs is virtually eliminated by an albumin concentration equivalent to 10% of that present in plasma. These recent findings suggest that the extent of plasma protein binding can affect the active secretion of drugs. The evidence presented herein strongly suggests that corrections should be applied for differences in plasma protein binding when predicting human renal clearance from rat and dog data.

The bias that is observed when predicting human renal clearance from either rat or dog renal clearance is in best accordance with interspecies differences in KBF and less so with GFR. The ratio of rat to human KBF is similar to the ratio of rat to human GFR and both are consistent with the bias observed between the two species. However, KBF is very similar between dog and human, 22 vs 16 mL/min/kg, which is consistent with the small bias of 1.3 (Table 2) obtained when predicting human renal clearance directly from dog and correcting for free fraction. GFR in dog is approximately two-fold greater than human and if this correction was applied would lead to an under-prediction of renal clearance in man. One may expect GFR to be appropriate for correcting compounds that undergo exclusively passive filtration,
however, the renal clearance of actively secreted compounds will be restricted by the flow of blood through the kidney rather than filtration through the glomerulus.

The excellent correlation that is observed between human and dog renal clearance, after corrections for plasma free fraction differences, suggests good species crossover between the transporters involved in any active processes for this diverse set of compounds. Renal clearance in the rat generally correlates well with man, however, certain organic anions appear to be outliers. Therefore, the extent of renal clearance in man may be under-predicted when using rat as a species for certain chemistries.

There is some evidence in the literature to suggest that rat may not have good crossover to man: Tahara et al have shown that there is a poor correlation between human and rat OAT3 mediated transport activities for nine substrates (Tahara et al, 2005). Also, Kato et al have shown that the renal clearance of a series of organic anions, which are all substrates for the organic anion transporting polypeptide 1 (oatp1), was much higher in female than in male rats (Kato et al, 2002). It was also shown that gene expression of oatp1, which is localised at the apical plasma membrane of the kidney, was higher in the kidneys of male rats. A large quantity of the literature rat renal clearance data used in this work was obtained from male rats. Therefore, one plausible hypothesis for the under-prediction of human renal clearance from rat, for the organic anions, is that re-uptake within the kidney is much lower in human relative to male rats. The disconnect between rat and human for the organic anions will distort predictions using simple allometry and Mahmood’s method, decreasing the accuracy of these two techniques, compared to the dog approach.

Finally, very little has been published to date on the prediction of human renal
clearance for organic anion compounds specifically. Mahmood applied his method to 10 molecules of which only 3 of these were acids and did not correct for differences in PPB. Moreover, Mahmood (2006) suggests that the free fraction corrected intercept method (FCIM) postulated by Tang et al. (2005) may not be suitable for renally secreted drugs. Our study shows that Mahmood’s approach is reasonably predictive, except for NSAIDs such as ibuprofen, as long as corrections are made for PPB differences. An analysis of our data using FCIM gave very similar statistics to Mahmood’s approach correcting for differences in PPB suggesting that FCIM is just as reasonable as Mahmood’s approach for predicting renally secreted drugs.

In the absence of species differences in PPB, laboratories would be best served to apply the direct correlation between human and dog renal clearance without the need for PPB data. When observing significant differences in PPB the data suggests that correcting for these differences is essential for predicting human renal clearance. This makes it particularly suitable for drug discovery, indeed, it permits an early screening of test compounds for their risk of exhibiting high renal clearance in dog, and hence in man. Moreover it also meets the requirement of reducing animal use. However, a caveat must be applied to this method when applied to test compounds which may exhibit or be suspected of having differences in renal transporter activity between dog and human.
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Author contribution

Participated in research design: Paine, McGinnity, and Riley.

Conducted experiments: Ménochet and Denton

Performed data analysis: Paine, McGinnity, and Denton.

Wrote or contributed to the writing of the manuscript: Paine and Riley.
References


Foot Notes

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Figure legends

Figure 1: Human unbound renal clearance versus rat (open) or dog (closed) unbound renal clearance. Acids (circle), bases (square), neutrals (triangle), zwitterions (diamond). Human GFR (solid line), dog GFR (dotted line), rat GFR (dashed line).

Figure 2: Measured human renal clearance versus measured renal clearance from (a) rat, (b) dog, (c) rat corrected for fu differences, (d) dog corrected for fu differences, (e) rat corrected for both KBF and fu differences, (f) dog corrected for both KBF and fu differences. Acids (circle), bases (square), neutrals (triangle), zwitterions (diamond).

Figure 3: Measured human renal clearance versus predicted renal clearance from (a) simple allometry, (b) simple allometry corrected for fu differences, (c) Mahmood renal allometry, (d) Mahmood renal allometry corrected for fu differences. Acids (circle), bases (square), neutrals (triangle), zwitterions (diamond).
Table 1

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**Table 2**

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</tr>
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<td>Dog</td>
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<td>1.3</td>
<td>0.84</td>
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<tr>
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<td>Dog</td>
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<td>1.1</td>
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Figure 1
Figure 3

3a

Measured human renal clearance (ml/min/kg)

Predicted from simple allometry (ml/min/kg)

3b

Predicted from simple allometry fu corr (ml/min/kg)

3c

Predicted from Mahmood allometry (ml/min/kg)

3d

Predicted from Mahmood allometry fu corr (ml/min/kg)