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Prediction of Human Drug Clearance Using a Single-Species, Fixed-Exponent Allometric Approach

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Background: Human pharmacokinetics can be predicted from animal data using the principle of allometry, which assumes a mathematical power-law relationship between pharmacokinetic parameters and body weights of animal species. The objective of the present study was to investigate the feasibility of extrapolating human drug clearance (*CL*) from a single animal species using simple allometry with a fixed body-weight exponent. **Methods:** *CL* values from rat, monkey, dog and human for 109 compounds were obtained from the literature. A normalization procedure based on the concept of a characteristic *CL* value was first introduced to homogenize and pool the *CL* data for a regression analysis. The allometric exponent from the regression analysis was then used as the exponent for *CL* extrapolation. The prediction performance of the proposed method was compared with methods that incorporate liver blood flow (LBF) or maximum lifespan potential (MLP). **Results:** An allometric exponent of 0.67 (95% CI, 0.64 to 0.71) adequately described the pooled *CL* data. A fixed value of 0.67 as the body-weight scaling exponent and monkey *CL* provided the best estimate of human *CL*, followed by rat and dog. *CL* prediction by the LBF approach was comparable to that of the fixed-exponent method. The MLP approach systematically underestimated the human *CL*. **Conclusions:** It is feasible to predict human drug *CL* from *CL* measured in a single animal species using simple allometry with a fixed body-weight exponent of 0.67. While monkey provides the best estimate of human *CL*, rat, but not dog, offers an acceptable prediction when monkey data are unavailable.

Key words: allometry, clearance, interspecies scaling, allometric scaling, pharmacokinetics

INTRODUCTION

A critical point in drug development is the transition between the preclinical and clinical phases, where decisions about the first-time-in-man dose are made.[1] The importance of the initial dose estimation cannot be overemphasized, since the safety of human subjects would be compromised if the dose were overestimated. Predictions involve a degree of uncertainty. In predicting the initial human dose from animals, one needs to integrate the best available animal data (pharmacokinetic, pharmacodynamic and toxicological) and to deal with the uncertainty problem that arises from the interspecies variability in ADME and drug actions. While extrapolation of pharmacodynamic and/or toxicological data to humans remains a difficult challenge, interspecies or allometric scaling of pharmacokinetics seems to be more tractable both experimentally and theoretically.

The literature is awash with studies that compare pharmacokinetic data among species based on the principle of allometric scaling, which assumes interspecies similarities in anatomy, physiology and biochemistry.[2-15] For many drugs, when their pharmacokinetic parameters in different animal species are plotted against animal body weights in a log-log plot, a linear relationship can be obtained. Therefore, if Y represents pharmacokinetic parameters and W represents body weights, a power function can be derived: $Y = a \bullet W^b$, where *a* and *b* are constants. This power function is known as the *allometric equation* and the two constants are referred to as the allometric coefficient (a) and the *allometric exponent* (or *body-weight exponent, b*), respectively.

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In the adaptation of allometry for prediction of drug behavior in humans, many methods have been suggested and their predictive performance rigorously analyzed.[16-19] It has been demonstrated that various correction factors may be needed for some specific drugs under certain circumstances.[16,19-23] However, a recent study based on a comprehensive analysis of 103 compounds suggested that prospective allometric scaling, with or without correction factors, was unreliable for estimating human clearance.[17,24] Further analyses of this data set by Ward and Smith led to the conclusion that allometric approaches using two or three of the preclinical species tended to predict human clearance less well as compared with methods based on clearance as a set fraction of liver blood flow from an individual species.[17] Furthermore, the allometric exponent and correlation coefficient of three-species allometry (rat, monkey, and dog) failed to determine whether the prediction would be successful.[17]

The utility of prospective allometric scaling has been questioned.[25] Apparently the center of criticism has been about the inherent uncertainty of prediction. The close examination of some outliers that do not follow an allometric relationship is of importance; however, the outliers as well might have obscured a fundamental question—that is, can we find certain regularity in allometric scaling of pharmacokinetics, which may form the basis for further application? In the present study we attempted to test this basic question using a large data set of drug clearance.

Theoretical considerations

Drug clearance varies extensively among drugs, spanning at least four orders of magnitude, and allometric scaling of clearance values produced an allometric exponent that had a mean value close to 0.67 or 0.75.[7] However, the exponent values for individual drugs were widely distributed, with values in the range of 0.3 to 1.2.[7] It is of interest to know whether uniform regularity exists for the highly variable *CL* data. Here we propose an approach to homogenize and then pool the *CL* data of various drugs.

We first assume for each drug the relationship between clearance (CL_i) and animal body weight (W_i) follows the allometric scaling law, which has the form of:

$$CL_i = aW_i^b \qquad \text{Eq.1}$$

, where a and b are the allometric coefficient and exponent, respectively. The subscript i (i = 1, 2, ⋯n) in Eq.1 denotes different species. Therefore,

$$\begin{aligned} CL_1 &= aW_1^b \\ CL_2 &= aW_2^b \\ &\cdots \\ CL_n &= aW_n^b \end{aligned} \qquad \text{Eq.2}$$

and

$$\prod_{i=1}^{n} CL_i = CL_1 \cdot CL_2 \cdots CL_n = a^n (W_1 \cdot W_2 \cdots W_n)^b = a^n \left(\prod_{i=1}^{n} W_i \right)^b \qquad \text{Eq.3}$$

The geometric mean clearance value for a given drug across species can then be expressed as

$$\overline{CL} = \left(\prod_{i=1}^{n} CL_i \right)^{1/n} \qquad \text{Eq.4}$$

, which according to Eq. 3 has the following form.

$$\overline{CL} = \left(\prod_{i=1}^{n} CL_i \right)^{1/n} = a \left(\prod_{i=1}^{n} W_i \right)^{b/n} = a \left(\overline{W} \right)^b \qquad \text{Eq.5}$$

, where $\overline{W} \equiv \left(\prod_{i=1}^{n} W_i \right)^{1/n}$ is the geometric mean body weight of all species considered. By normalizing the clearance in each animal species (Eq.1) to their geometric mean (Eq.5) and replacing CL_i and W_i for CL and W, respectively, the following relationship is then obtained.

$$CL \Big/ \overline{CL} = \left(\overline{W} \right)^{-b} W^b \qquad \text{Eq.6}$$

or

$$\log \left(CL \Big/ \overline{CL} \right) = -b \cdot \log \overline{W} + b \cdot \log W \qquad \text{Eq.7}$$

The geometric, species-averaged clearance, $\overline{CL}$, can be considered as the characteristic clearance value for each individual drug in a hypothetical "reference animal species" whose body weight is the geometric mean of those of all animals of interest, i.e. rat, monkey, dog, and human in this study. Therefore, the magnitude of the species-averaged clearance manifests drug-specific pharmacokinetic properties in the reference species. If the allometric assumption approximately holds for each drug, Eq.7 will predict the same b value from both the slope and the intercept of a pooled $\log \left(CL \Big/ \overline{CL} \right)$ -versus-*log* W plot, i.e.

$$b = \text{slope} = -\left(\text{intercept} \Big/ \log \overline{W} \right) \qquad \text{Eq.8}$$

METHODS

Data collection

Clearance values for 109 xenobiotics included the 103-compound dataset of Ward and Smith[17,26] augmented by six other substances (see Appendix); three protein drugs (interferon α, [27,28] lenercept,[29] recombinant tissue plasminogen activator[30]) and three small molecules (grepafloxacin,[31,32] garenoxacin,[33] indinavir[34,35]). Total, systemic plasma or serum *CL* values were available for the 109 compounds in rat, monkey, dog, and human. No restrictions were placed on sex or on the rat or dog strain.[17] The monkey data were mostly from rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) species.[17]

Data analysis

1. Data transformation and regression

The representative body weight for each species was chosen as: rat, 0.33 kg; monkey, 5 kg; dog, 12 kg; human, 70 kg. For each drug, the recorded *CL* value (ml/min/kg body weight) for each species was multiplied by its representative body weight to obtain a *CL* value in ml/min, which was then divided by the geometric mean *CL* value of the four species to give a normalized *CL* value. For example, the normalized, dimensionless *CL* for a particular drug in rats (CL_{rat}^{norm}) can be obtained as:

$$CL_{rat}^{norm} = CL_{rat} \Big/ \overline{CL} \qquad \text{Eq.9}$$

, where $\overline{CL}$ according to the definition in Eq.4 has the following form.

$$\overline{CL} = (CL_{rat} \cdot CL_{monkey} \cdot CL_{dog} \cdot CL_{human})^{1/4} \qquad \text{Eq.10}$$

After the normalization procedure, a total of 436 normalized CL, body-weight data points (109 compounds×4 species) were pooled and plotted on log-log coordinates. A least-squares linear regression of Eq.7 was then fitted to the combined log-log transformed data.

2. Prediction methods

Three methods were used for predicting human *CL* from preclinical animal species.

Method I. The fixed-exponent approach

This proposed scaling method in the present investigation used body-weight (*W*) based simple allometry, with a fixed scaling exponent, i.e.,

$$CL_{human}(\text{ml/min}) = CL_{animal}\left(\frac{W_{human}}{W_{animal}}\right)^{b} \qquad \text{Eq.11}$$

The exponent (b) was fixed at 0.67 for all drugs, based on the pooled analysis.

Method II. The liver-blood-flow (LBF) approach[17]

The monkey LBF method, the most accurate method reported in Ward and Smith's study,[17] was included for the purpose of comparison.

$$CL_{human}(\text{ml/min}) = CL_{monkey}\left(\frac{LBF_{human}}{LBF_{monkey}}\right) \qquad \text{Eq.12}$$

The LBF values of 45 and 21 ml/min/kg were used for monkeys and humans,[36] respectively.

Method III. The maximum-life-span-potential (MLP) approach[37]

The monkey MLP approach, previously reported to be a better approach for single-species extrapolation,[37] was also included for comparison.

$$CL_{human}(\text{ml/min}) = CL_{monkey}\left(\frac{W_{human}}{W_{monkey}}\right)\cdot\left(\frac{MLP_{monkey}}{MLP_{human}}\right) \qquad \text{Eq.13}$$

The MLP values of 22 and 93 years were used for monkeys and humans, respectively.[36]

3. Prediction performance

Several approaches were used to assess the prediction performance of each prediction method. The fold-error (FE) between predicted and observed CL was calculated as:

$$\text{FE} = \frac{CL_{predicted}}{CL_{observed}} \qquad \text{Eq.14}$$

For quantitative comparison, the average-fold-error (AFE) and the root-mean-squared-error (RMSE) were defined and calculated as[38,39]:

$$\text{AFE} = 10^{\left|\frac{\sum \log(\text{FE})}{\text{N}}\right|} \qquad \text{Eq.15}$$

$$\text{RMSE} = \sqrt{\frac{\sum (CL_{predicted} - CL_{observed})^2}{N}} \cdot \qquad \text{Eq.16}$$

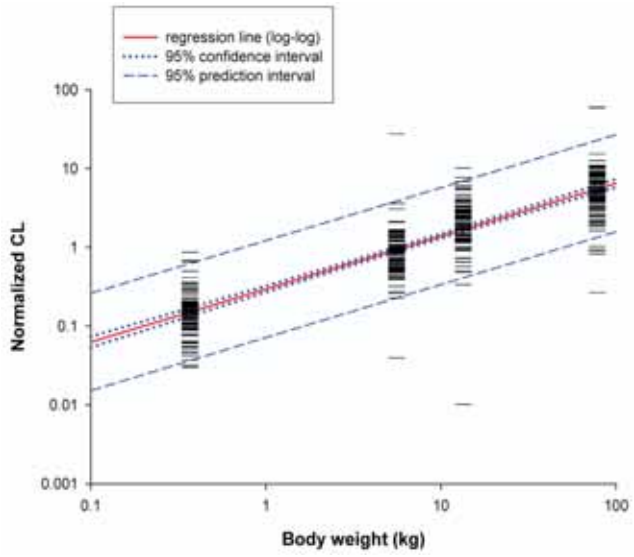

Fig.1 Dimensionless, normalized clearance (horizontal marks) as a function of body weight (kg) for 109 compounds in rat, monkey, dog and human.

A method that makes a perfect prediction would have an AFE value equal to 1. An AFE value of 2 suggests that the prediction was on average 2-fold off (100% above or 50% below). A better prediction method would have an AFE value close to 1, with a minimized RMSE values. Accordingly, the product AFE×RMSE was used as a composite metric of overall performance.

RESULTS

The proposed normalization procedure was applied to 436 *CL* values (109 compounds×4 species) in a log-log plot, to which a least-squares linear regression was applied (Fig. 1). The fitted slope and the intercept, according to Eq.7, are 0.67 and -0.53, respectively (Table 1). The 95% confidence interval of the slope is 0.64 - 0.71 (Table 1), suggesting that the exponent b value for the pooled data is highly constrained. The b value was also estimated from the intercept and the geometric mean body weight (6.1 kg), according to Eq.8, which gave a value of 0.67 with a 95% CI of 0.62 - 0.72, consistent with the values estimated from the slope (Table 1). To further analyze the data, the normalized *CL* values in each species were divided by the corresponding $W^{0.67}$, from which the frequency distribution of the transformed *CL* values in each species was constructed, Fig.2. The $W^{0.67}$-standardized values for each species superimposed and are log-normally distributed.

Table 1 Data characteristics and fitting results according to Eq.7

No. of drugs	Animal species (kg)	No. of *CL* values	Geometric mean body weight of species, $\overline{W}$ (kg)	Slope (95% C.I.)
109	rats (0.33), monkeys (5), dogs (12), humans (70)	436	6.1	0.67 (0.64, 0.71)

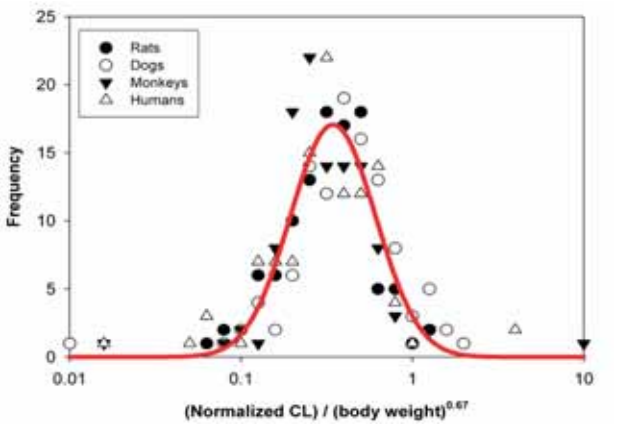

Fig. 2 Frequency distribution of normalized CL data expressed on a per $W^{0.67}$ basis for the four species. The line represents the lognormal distribution fitted to all data.

Fig.3 quantitatively compares the prediction performance among various methods. The monkey LBF and the monkey MLP methods were included for comparison because both have been shown in the previous studies[17,37] to provide better prediction. Among various methods compared, the monkey 0.67-fixed-exponent and the rat 0.67-fixed-exponent methods have the lowest average-fold-error (AFE) values, which are very close to 1 (Fig.3). Furthermore, the monkey 0.67-fixed-exponent and LBF methods show the lowest root-mean-squared-error (RMSE) values. Accordingly, the results in Fig.3 suggest that the monkey 0.67-fixed-exponent method is superior to the others. The robustness of the prediction performance was tested using 10 subsets of compounds, where, for each subset, 10 compounds were randomly selected from the 109-compound data set. Table 2 summarizes the prediction performance of five methods for the 10 sub sets. For the 10 sub sets, the monkey fixed-exponent approach has the lowest AFE×RMSE product in 5 sub

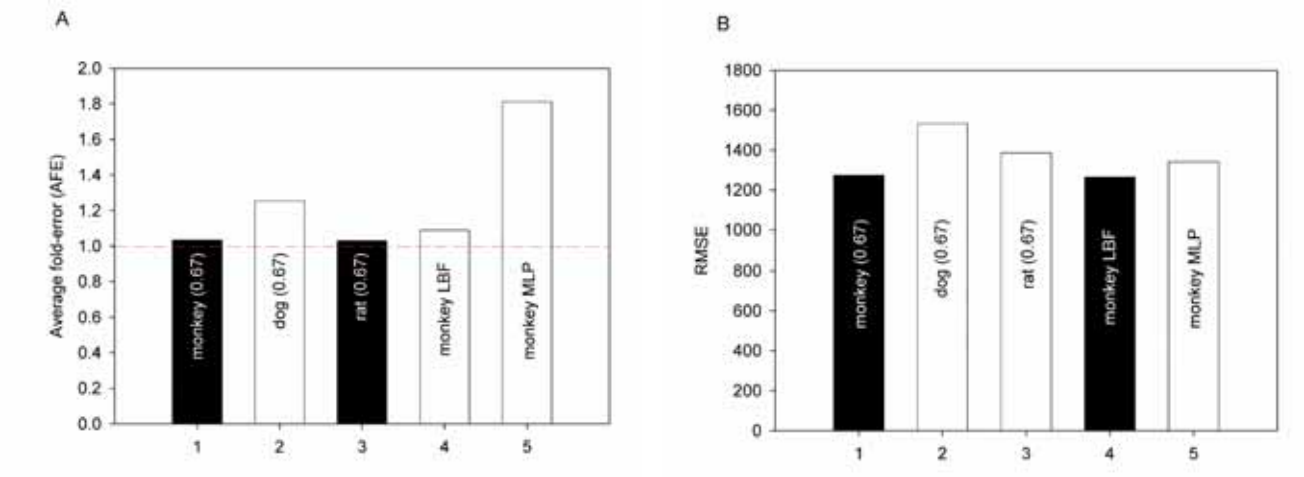

Fig. 3 Comparison of prediction performance among various methods. (A) Average-fold-error (AFE) (B) Root-mean-squared-error (RMSE)

Table 2 Comparison of prediction performance in ten randomly sampled datasets*

Subset	Monkey (0.67)			Dog (0.67)			Rat (0.67)			Monkey LBF			Monkey MLP		
	AFE	RMSE	AFE×RMSE	AFE	RMSE	AFE×RMSE	AFE	RMSE	AFE×RMSE	AFE	RMSE	AFE×RMSE	AFE	RMSE	AFE×RMSE
A	1.11	176	**195§**	1.33	342	455	1.12	357	400	1.25	198	248	1.58	258	408
B	1.54	387	**596**	1.14	687	783	1.02	954	973	1.37	509	697	2.70	442	1193
C	1.18	507	598	2.39	1953	4668	1.19	355	**422**	1.33	551	733	1.49	382	569
D	1.21	496	600	1.25	521	651	1.06	557	590	1.08	521	**563**	2.12	425	901
E	1.11	180	**200**	1.64	1181	1937	1.69	940	1589	1.25	672	840	1.57	489	768
F	1.40	582	815	1.22	1235	1507	1.07	753	**806**	1.25	740	925	2.46	490	1205
G	1.02	630	**643**	1.47	2271	3338	1.95	721	1406	1.10	954	1049	1.79	578	1035
H	1.58	487	769	1.47	1041	1530	1.46	532	777	1.40	529	**741**	2.76	433	1195
I	1.51	440	664	1.55	673	1043	1.02	278	**284**	1.70	457	777	1.16	305	354
J	1.05	602	**632**	1.61	2135	3437	1.13	575	650	1.18	649	766	1.67	490	818
mean ¶			**519**			1501			692			693			779

* Ten subsets (A-J) of CL data were randomly sampled from the 109-compound data set. Each subset consists of 10 drugs.

§ Numbers in bold face represent the lowest among various methods in each subset.

¶ Geometric mean

sets, followed by the rat fixed-exponent approach (3 sub sets) and the monkey LBF approach (2 sub sets) (Table 2). Overall, the monkey 0.67-fixed-exponent approach shows the most promising prediction profile (Table 2). To further compare methods in which monkeys are the common species, a plot for the comparison of prediction outcome (fold-error) was constructed (Fig.4). While the monkey fixed-exponent and the monkey LBF approach are almost identical in prediction (Fig.4), the comparison between the monkey MLP and the fixed-exponent method is far below the line of identity (Fig.4), suggesting that the monkey MLP method tends to underestimate human *CL*.

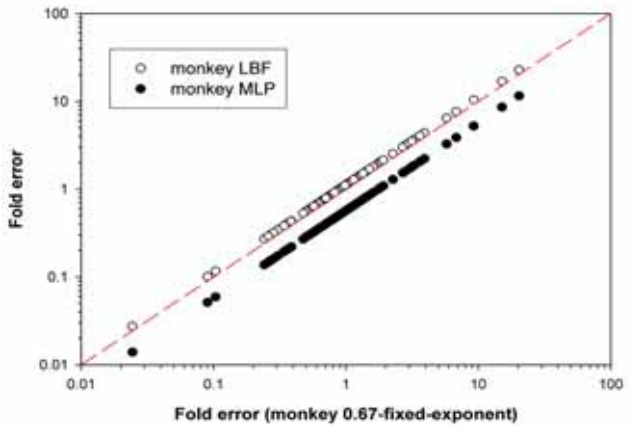

Fig.4 Comparison among monkey-based methods. The dashed line represents the line of identity.

DISCUSSION

Much recent progress has been made in applying the allometric scaling principle to extrapolate human drug *CL* from animal *CL* values. At least ten approaches have been proposed for estimation of human *CL* using data from preclinical animal species.[19] The prediction performance of the various approaches has been tested in large data sets that encompass more than 100 compounds.[17,18,24] A recent study has shown that simple allometry based on two or three animal species appears to be inadequate for predicting human *CL*.[17] It is therefore tempting to extrapolate human pharmacokinetics from a single animal species.[17,37,40-43]

The present study was initiated by two questions raised. First, given the highly variable characteristics of *CL* data, can one find a general scaling relationship between the commonly used preclinical species (rat, monkey, dog) and human? Second, if one is to use single species to extrapolate human *CL* using simple body-weight allometry, what will be the most appropriate species and scaling exponent? The answer to the first question may shed some light on the second question.

To address the first question, we employed a novel approach to synthesize the *CL* data, of various drugs in different species, which, at first sight, seemed so variable to find any regularity at all. The concept of drug disposition and elimination in a "hypothetical reference species" that shares common traits of the animal species interested (i.e. rat, monkey, dog and human) was, for the first time, introduced. Therefore, every drug would have its own characteristic *CL* value—whose magnitude is dependent on the physicochemical and/or pharmacokinetic properties of the drug—in the reference species. Since drug *CL* among species was assumed to be a power law function of body weight, we defined the characteristic *CL* value for a drug as the geometric mean of each individual *CL* value in different species, as suggested in Eq.4.

The results in Table 1 suggest that certain regularity may exist for the seemingly chaotic data, to which the 0.67-power law of allometric scaling tends to apply (Table 1). The almost superimposed lognormal distribution of the $W^{0.67}$-standardized data further supports the premise (Fig.2). Apparently, the proposed concept of characteristic CL, and the normalization procedure thus derived, seemed to be effective for homogenizing the data, thereby leading to the current finding.

Strikingly, the exponent value (0.67) reported in the current analysis is different from the prevailing exponent value (0.75) found in a previous study.[7] While there is a continuous disagreement, even up to now, about which value (i.e. 0.67 vs. 0.75) should prevail in the field of biology,[44-46] we attempt to offer one possible explanation about the discrepancy. The animal species included in the previous study covered 18 species whose body weights spanned approximately 5 orders of magnitude,[7] while the present study limited the species only to 4 mammals with the range of body weight covering only 2 orders of magnitude. It has been shown that the range of body size may affect the exponent measured.[47-50]

Rather than explore the controversial issue about the general law of scaling, we approached the problem from a practical point of view. On the one hand we well recognized and accepted the fact that it is quite easy to find exceptional cases or outliers that do not follow any scaling law at all; on the other we were searching for the exponent that would best describe the available data set. The exponent thus obtained can then serve for the next purpose, which is to extrapolate human *CL* from a single species using simple body-weight allometry with a common exponent. Some major findings are summarized here. First, among the three commonly used preclinical animals, monkey provides the best estimate of human *CL* using the 0.67-fixed-exponent approach. Dog, however, offers the least accurate estimation. Rat in general seems to perform about as well as monkey. Second, when monkey is considered as the species for scaling, the 0.67-fixed-exponent approach tends to be the most optimal, followed by the LBF approach. In contrast, the MLP approach appears to systematically underestimate *CL*. Finally, it is of interest to note that a linear relationship was found between the fixed-exponent and LBF and MLP methods (Fig.4). Since all three methods predict the

human *CL* based on the *CL* of monkey multiplied by a factor that is some function of the body weight of human and monkey (Eqs.11-13), the finding may not be too surprising. However, we reason that Ward and Smith's LBF method is somehow a fixed-exponent approach *per se*, given that liver blood flow follows the allometric scaling relationship,[2] i.e. $LBF \propto W^b$.

Therefore, Eq.12 becomes

$$CL_{human}(ml/\min) = CL_{monkey}\left(\frac{LBF_{human}}{LBF_{monkey}}\right) = CL_{monkey}\left(\frac{W_{human}}{W_{monkey}}\right)^b$$

Eq.17

Based on the values of liver blood flow used, 1470 ml/min and 225 ml/min for a 70-kg human and a 5-kg monkey respectively, in the present and Ward and Smith's analysis,[17] the estimated *b* value would be equal to 0.71. It then becomes evident as to why LBF method provided systematically higher estimates than the 0.67-fixed-exponent approach (Fig.4). Furthermore, the above analysis gives us an idea about where a method based on the 3/4-power law would stand.

In the present study, we conducted a novel analysis to show that a single-species, 0.67-fixed-exponent allometric approach may be suitable for predicting human drug clearance. The emphasis has been on the derivation of the method based on a retrospective data set. Several caveats, however, should be mentioned. The proposed method is limited to prediction of total systemic clearance for intravenous administration of drugs. When predicting oral clearance is desired, bioavailability information of a drug should also be collected or predicted. Many factors can affect prediction results, including, but not limited to, route of elimination, plasma protein binding and hepatic extraction ratio. Species differences in these factors should be considered and appropriate corrections made to improve prediction.[38]

In summary, the present study introduced a novel approach to analyze a comprehensive *CL* dataset of 109 compounds. We were able to identify an allometric exponent of 0.67 that best described the combined 436 *CL* data in rat, monkey, dog and human. Our study demonstrates the applicability of extrapolating human *CL* from a single animal species using simple allometry with a fixed exponent of 0.67. The finding of this study therefore supports the use of the exponent value 0.67, as set forth in the FDA guidance,[51] in predicting human dose from animal data. While the present study shows that monkey *CL* values would generally provide the best estimate of human *CL* using the fixed exponent approach, rat, but not dog, is a suitable alternative species when data from monkey are not available.

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APPENDIX

Clearance values for 103 compounds (the Ward-Smith dataset) can be found in Reference 26. Clearance values for six additional compounds are listed in Table A1.

Table A1 Clearance values (mL/min/kg) of six additional compounds used in the current analysis.

Compound	Rat	Dog	Monkey	Human
Interferon alpha	3.6	1.6	2.6	2.8
Lenercept	0.0070	0.0086	0.0080	0.0047
rt-PA*	26.3	15.3	9.32	8.16
Grepafloxacin	24.1	6.04	5.41	6.60
Garenoxacin	12.1	2.43	3.39	1.23
Indinavir	107	16.0	36.0	18.2

* recombinant tissue plasminogen activator

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