

Extrapolating Human Drug Clearance from a Single Animal Species Using the Allometric Principle with a Fixed Scaling Exponent

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Introduction

Background and Objectives

- Allometric scaling (AS) in biology: no consensus on the allometric exponent
 - 0.67 (surface law) vs. 0.75 (quarter power law)
- AS in PK: the scaling exponent varies; for CL, from <0.5 to >1.0
- AS for PK prediction
 - works perfectly for some drugs, but failure is not uncommon
 - prospective use has been questioned
- Controversies and practical issues
 - multiple species vs. single species; which species?
 - correction factors
- Motivations
 - FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005). "...body surface area correction factors (i.e., $W^{0.67}$) should be maintained for selecting starting doses for initial studies in adult healthy volunteers."
 - Ward and Smith (2004): "...recommend that liver blood flow-based extrapolation from monkey be used for the most accurate and reliable estimation of human clearance."
- Objectives
 - to revisit the scaling exponent for CL by applying a novel approach to a large CL dataset
 - to evaluate different single-species method for extrapolating human drug CL

Methods

- Dataset:
 - Ward & Smith 103-compound CL dataset for rats, dogs, monkeys and humans plus a dataset for 6 additional compounds; a total of 109 compounds
 - Human CL prediction methods
 - Simple allometry (Eq.1)
 - Monkey liver blood flow (LBF) (Eq.2)
 - Monkey maximum life-span potential (MLP) (Eq.3)
 - Prediction performance
 - Fold error (FE)
 - Average fold-error (AFE)
 - Root mean-squared error (RMSE)
- $$(Eq.1) \quad CL_{human} (ml/min) = CL_{animal} \left(\frac{W_{human}}{W_{animal}} \right)^b$$
- $$(Eq.2) \quad CL_{human} (ml/min) = CL_{monkey} \left(\frac{LBF_{human}}{LBF_{monkey}} \right)^b \quad \text{(Ward & Smith, Drug Metab. Dispos. 2004;32:603-611.)}$$
- $$(Eq.3) \quad CL_{human} (ml/min) = CL_{monkey} \left(\frac{W_{human}}{W_{monkey}} \right)^b \cdot \left(\frac{MLP_{monkey}}{MLP_{human}} \right)^c \quad \text{(Campbell, Drug Info. J. 1994;28:235-245.)}$$
- $$FE = \frac{CL_{predicted}}{CL_{observed}} \quad AFE = 10^{\frac{\sum |\log FE|}{N}} \quad RMSE = \sqrt{\frac{\sum (CL_{predicted} - CL_{observed})^2}{N}}$$

Results

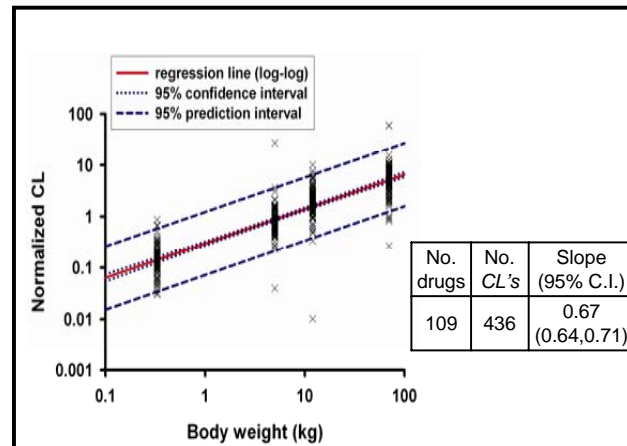


Fig.1 Normalized CL values in rats, monkeys, dogs and humans for 109 compounds vs. species body weight.
In this 109-compound dataset, each drug has a CL value in the four species. The representative body weight for each species was chosen as: rat, 0.33 kg; monkey, 5 kg; dog, 12 kg; human, 70 kg. For 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 can be obtained as (See Appendix):

$$\text{where } CL_{rat}^{normalized} = \frac{CL_{rat}}{\bar{CL}} \quad \bar{CL} = (CL_{rat} \cdot CL_{monkey} \cdot CL_{dog} \cdot CL_{human})^{1/4}$$

After the normalization procedure, a total of 436 (normalized CL, body-weight) data points (109 compounds \times 4 species) were pooled and plotted on log-log coordinates. A least-squares linear regression was applied to the pooled log-log transformed data, according to Eq. A5.

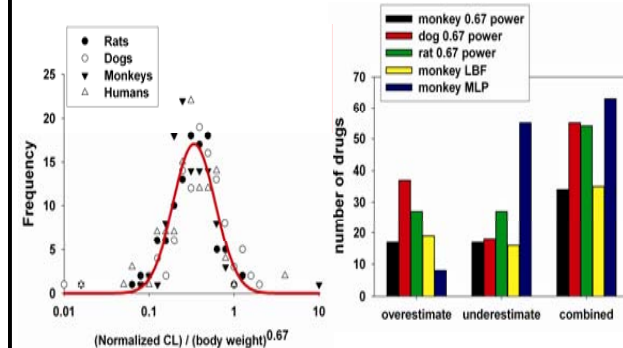


Fig.2 Frequency distribution of normalized CL data expressed on a per $W^{0.67}$ basis for the four species. The frequency represents the number of drugs whose normalized CL data fall within pre-defined log bins. The line represents the lognormal distribution fitted to all data.

Fig.3 Accuracy of various single-species methods at predicting human CL. Overestimate: FE >2; Underestimate: FE <0.5; Combined: over + under. Total number of drugs: 109

Results

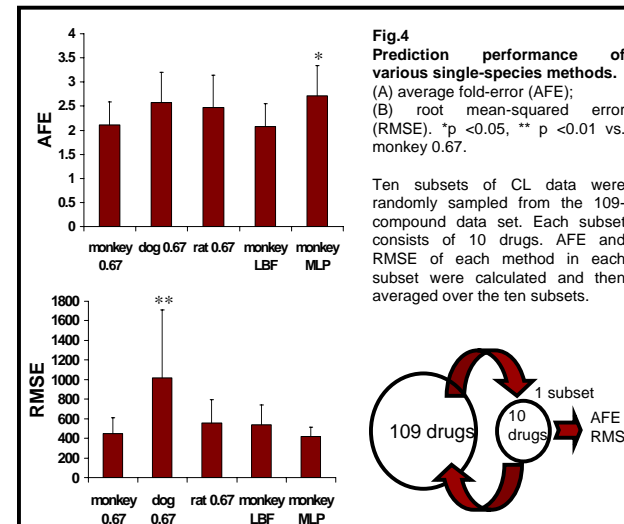


Fig.4 Prediction performance of various single-species methods. (A) average fold-error (AFE); (B) root mean-squared error (RMSE). *p <0.05, ** p <0.01 vs. monkey 0.67.

Ten subsets of CL data were randomly sampled from the 109-compound data set. Each subset consists of 10 drugs. AFE and RMSE of each method in each subset were calculated and then averaged over the ten subsets.

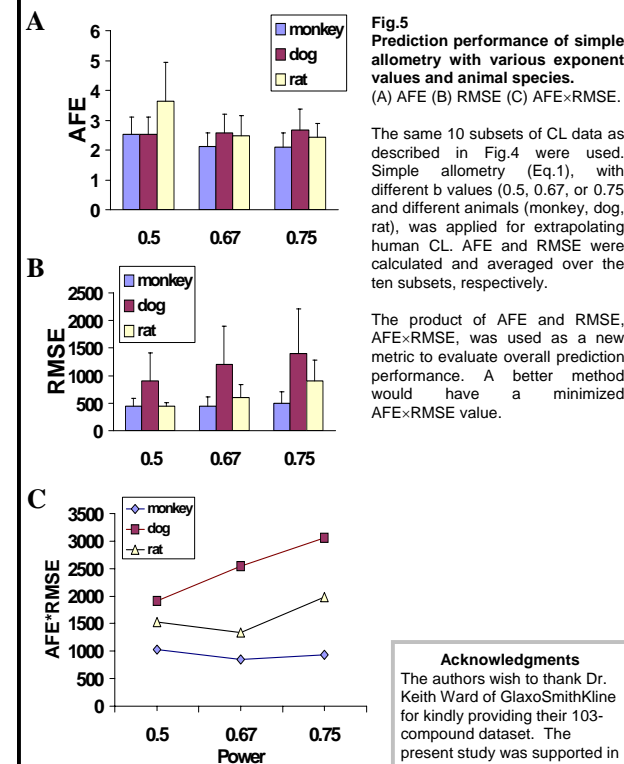


Fig.5 Prediction performance of simple allometry with various exponent values and animal species. (A) AFE (B) RMSE (C) AFE*RMSE.

The same 10 subsets of CL data as described in Fig.4 were used. Simple allometry (Eq.1), with different b values (0.5, 0.67, or 0.75) and different animals (monkey, dog, rat), was applied for extrapolating human CL. AFE and RMSE were calculated and averaged over the ten subsets, respectively.

The product of AFE and RMSE, AFE*RMSE, was used as a new metric to evaluate overall prediction performance. A better method would have a minimized AFE*RMSE value.

Acknowledgments

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Summary

- A novel approach was introduced to revisit scaling exponent for CL in a large data set containing CL values of 109 compounds in rats, dogs, monkeys, and humans.
- An allometric exponent of 0.67 (95% CI, 0.64 to 0.71) adequately described the pooled 436 CL values, thereby providing a basis for the use of body surface area correction factors (i.e., $W^{0.67}$) in selecting starting dose in humans.
- When 0.67 was used as the body-weight scaling exponent, the prediction of human CL based on dog data tended to be less accurate and quantitatively the most biased of all data evaluated.
- When the monkey CL was used for prediction, the 0.67-power simple allometry method and the liver-blood-flow (LBF) method have comparable prediction performance, given the fact that LBF follows allometric scaling relationship.
- The monkey maximum life-span potential (MLP) method systematically underestimate the human CL.
- The prediction from monkey data was less sensitive to the choice of scaling exponents, while dog data have the most sensitive dependence on the scaling exponent used.

Appendix

Derivation of equations

Drug clearance varies extensively among drugs, spanning at least four orders of magnitude, and allometric scaling of clearance values produced a body-weight exponent that had a mean value close to 0.67 or 0.75. However, the exponent values for individual drugs were widely distributed, with values in the range of 0.3 to 1.2. 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 Eq. A1,

$$CL_i = aW_i^b \quad (Eq. A1)$$

where a and b are the allometric coefficient and exponent, respectively. The subscript i ($i = 1, 2, \dots, n$) in Eq. A1 denotes different species. Therefore,

$$\prod_{i=1}^n CL_i = CL_1 \cdot CL_2 \cdot \dots \cdot CL_n = a^n (W_1 \cdot W_2 \cdot \dots \cdot W_n)^b = a^n \left(\prod_{i=1}^n W_i \right)^b \quad (Eq. A2)$$

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

$$\bar{CL} = \left(\prod_{i=1}^n CL_i \right)^{1/n} = a \left(\prod_{i=1}^n W_i \right)^{b/n} = a(\bar{W})^b \quad (Eq. A3)$$

By normalizing the clearance in each animal species (Eq. A1) to their geometric mean (Eq. A3) and dropping the subscript i , the following relationship is then obtained.

$$\frac{CL_i}{\bar{CL}} = \left(\frac{W_i}{\bar{W}} \right)^b \quad (Eq. A4)$$

The geometric, species-averaged clearance 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. In this case, pharmacokinetic variability among various drugs might be minimized by the normalizing procedure suggested by Eq. A4. Accordingly, the CL data of various drugs might be pooled for analysis.

$$\log \left(\frac{CL_i}{\bar{CL}} \right) = -b \cdot \log \bar{W} + b \cdot \log W \quad (Eq. A5)$$