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A Mathematical Description of the Functionality of Correction Factors Used in Allometry for Predicting Human Drug Clearance

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Abbreviations: PK, pharmacokinetics; CL, clearance; MLP, maximum life-span potential; BrW, brain weight; ROE, rule of exponents

Abstract

The functionality of the correction factors, maximum life-span potential (MLP) and brain weight (BrW) used in allometry, is mathematically described. Correction by MLP or BrW is equivalent to a multiplication of some constants by the predicted values in humans from simple allometry, but they have no relationship to measured pharmacokinetic parameters in the animal species. The values of these constants (F_{MLP} or F_{BrW}) were calculated for some commonly used combinations of animal species. For all combinations of animal species, the value of F_{BrW} is always greater than F_{MLP} with a fold-increase of about 1.3 to 1.9. Different combinations of species give different values of F_{BrW} and F_{MLP}. In addition, the role of correction factors (MLP and BrW) or the "rule of exponents" (ROE) was evaluated. An intrinsic defect in using correction factors or ROE was revealed; different study designs will produce significantly different prediction results. However, ROE may still serve as a useful practical approach in predicting human CL since it was derived from real observations and has been applied to many examples.

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Introduction

Allometric scaling is one of the most widely used approaches in predicting human pharmacokinetic (PK) parameters (CL, V_d, $t_{1/2}$) from animals. The allometric relationship has been observed to follow the power function: parameter = *a* (body weight) ^{b}, where *a* and *b* are a coefficient and an exponent, respectively. The power function is empirical and it produces prediction errors that are observed in practice. Therefore, various modifications have been proposed to improve these predictions, including: *in vitro* correction (Lave, et al., 1997); two-term power function approach (Boxenbaum and Fertig, 1984); maximum life-span potential (MLP) or brain weight (BrW) correction (Mahmood and Balian, 1996b); rule of exponents (ROE) (Mahmood and Balian, 1996a); unbound CL approach (Feng, et al., 2000). Among these modifications, ROE appears to be widely used in industry. ROE states: 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 is applied. ROE is based on empirical observations and it suggests that when a large exponent is observed (greater than the generally observed exponent, 0.75), it is likely that CL will be over-predicted. A MLP or BrW correction is thus used to lower this potential over-predicted value. Interestingly, some recent studies by Ward *et al.* indicated that ROE did not show any advantage over approaches with or without other correction factors. Furthermore, Ward *et al.* showed that the prediction of CL based on the monkey liver blood flow (LBF) method was superior to ROE (Ward and Smith, 2004;Nagilla and Ward, 2004). This controversy remains unresolved.

The current work was not designed to solve this controversy or judge which approach is superior. In a previous study (Tang and Mayersohn, submitted for publication), a general

allometric equation (GAE) was derived, which is equivalent to the approach used to obtain predicted CL in humans by performing a log-log transformation of the power function followed by linear regression. Based on the GAE, we recognized the functional relationship for the aforementioned correction factors (MLP and BrW) used in allometry. In addition, methods of MLP correction, BrW correction and ROE used in allometric scaling were evaluated based on those observations.

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Methods

Theory

The function relating predicted PK parameters in humans ($P_{predicted}$) to animal body weights (W) and observed animal PK parameters (P) was derived from our previous study (Tang and Mayersohn, submitted for publication), and is presented in Equation (1),

$$P_{predicted} = \prod_{i=1}^{n} P_i^{(A_i + 1.845B_i)} \quad (1)$$

where:

n different animal species are used in allometric scaling

P_i is the value of the PK parameter in the i^{th} animal species

$$A_i = \frac{1}{n}(1 - B_i \bullet \log \prod_{j=1}^{n} W_j)$$

$$B_i = \frac{1}{n} \bullet \frac{\log\left[\dfrac{W_i^{n-1}}{\prod_{\substack{k=1 \\ k\neq i}}^{n} W_k}\right]}{\sum_{k=1}^{n}\left[\log W_k - \dfrac{\log \prod_{l=1}^{n} W_l}{n}\right]^2}$$

W is the body weight of a specified animal species

The scaling of MLP-corrected CL, thus, is equivalent to,

$$(P_{predicted} \cdot MLP_{human}) = \prod_{i=1}^{n} (P_i \cdot MLP_i)^{(A_i + 1.845B_i)} \quad (2)$$

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which is further equivalent to,

$$P_{predicted} = \frac{\prod_{i=1}^{n} MLP_i^{(A_i + 1.845B_i)}}{MLP_{human}} \cdot \prod_{i=1}^{n} P_i^{(A_i + 1.845B_i)} = F_{MLP} \cdot \prod_{i=1}^{n} P_i^{(A_i + 1.845B_i)} \quad (3)$$

where,

$$F_{MLP} = \frac{\prod_{i=1}^{n} MLP_i^{(A_i + 1.845B_i)}}{MLP_{human}} \quad (4)$$

The scaling of BrW-corrected CL, thus, is equivalent to,

$$(P_{predicted} \cdot BrW_{human}) = \prod_{i=1}^{n} (P_i \cdot BrW_i)^{(A_i + 1.845B_i)} \quad (5)$$

which is further equivalent to,

$$P_{predicted} = \frac{\prod_{i=1}^{n} BrW_i^{(A_i + 1.845B_i)}}{BrW_{human}} \cdot \prod_{i=1}^{n} P_i^{(A_i + 1.845B_i)} = F_{BrW} \cdot \prod_{i=1}^{n} P_i^{(A_i + 1.845B_i)} \quad (6)$$

where,

$$F_{BrW} = \frac{\prod_{i=1}^{n} BrW_i^{(A_i + 1.845B_i)}}{BrW_{human}} \quad (7)$$

The common values for W, MLP and BrW of animal species are listed in Table 1. MLP and BrW were calculated from body weight according to the literature (Boxenbaum, 1982). All the mathematical equations were programmed in MATLAB 6.5 (The MathWorks, Inc., Natick, MA).

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Results

It can be seen that the first part of Equations (3) and (6), that F_{MLP} and F_{BrW}, are only dependent on the combinations of animal species selected, since body weight, MLP and BrW in each animal species are fixed constants. The second part of the equation, $\prod_{i=1}^{n}(P_i \cdot BrW_i)^{(A_i+1.845B_i)}$, is, in fact, the predicted value in humans obtained from simple allometry. The above analyses clearly indicate that the functionality of the correction factors, MLP and BrW, as used in allometry, is actually a multiplication of some constants by the predicted values in humans obtained from simple allometry and has no bearing on measured PK parameters in the animal species. Those values of F_{MLP} and F_{BrW} for some common combinations of animal species are calculated and presented in Table 2.

Several conclusions may be reached on the basis of this analysis. First, the values of F_{MLP} vary from 0.33 to 0.62, which means that the predicted value based upon a MLP correction is about 1/3 to 2/3 of the predicted value from simple allometry, depending on the combination of species examined. The values of F_{BrW} vary from 0.17 to 0.47, which means that the predicted value based upon a BrW correction is about 1/5 to 1/2 of the predicted value from simple allometry, depending on the combination of species.

Second, for all combinations of animal species, the value of F_{BrW} is always greater than F_{MLP} with a fold-increase of about 1.3 to 1.9. In another words, the magnitude of the correction by BrW is always greater than that by MLP. This phenomenon, that is the observed larger magnitude of correction by the BrW method than by the MLP method, is theoretically proven here.

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Finally, different combinations of species give different values for F_{BrW} or F_{MLP} (Table 2). The most significant difference is that between the combination of (mouse, rat, dog) and (mouse, rat, monkey), which represents almost a two-fold difference by replacing the dog with the monkey.

Discussion

The functionality of the correction factors, MLP and BrW, is described here mathematically for the first time. The correction with MLP and BrW in allometry is actually equivalent to multiplying some fixed constants by the values predicted from simple allometry. This statement also reveals an important fact; that prior to the experiments to obtain PK parameters in each animal species, the magnitude of correction by MLP or BrW has already been fixed once the combination of animal species has been chosen. Based on the above statements, we can evaluate the role of correction factors (MLP and BrW) or ROE.

First, we can ask whether it is reasonable that the magnitude of correction by MLP or BrW is fixed once the combination of animal species is chosen, no matter what experimental values are measured in animals and no matter what exponents are obtained from simple allometry. For example, assuming that using the same combination of animal species the exponents from simple allometry for drug A and drug B are 0.71 and 0.99, respectively. As illustrated above the magnitude of correction for both drugs using MLP correction is the same. Is this reasonable?

Second, we can ask whether it is reasonable that the magnitude of correction is only dependent on the animal species selected. There are numerous drugs whose PK parameters follow a good allometric relationship across animal species. The prediction of the PK parameters for those drugs, according to the MLP, BrW or ROE correction methods, would be totally different if other animal species were used. For example, assume that the mouse, rat, monkey and dog are available species for experimentation with those drugs. One group of investigators chooses mouse, rat and monkey and obtains exponents between 0.71 and 0.99 or greater than 1.00. The other group chooses the mouse, rat and dog and this should result in the same

exponents. The first group would correct the predicted value from simple allometry by 0.62, if the exponents are between 0.71 and 0.99 (therefore, corrected by the MLP method) or by 0.47 if the exponents are greater than 1.00 (therefore, corrected by the BrW method). In contrast, the second group would correct the predicted value from simple allometry by 0.32 if the exponents are between 0.71 and 0.99 (therefore, corrected by the MLP method) or by 0.17 if the exponents are greater than 1.00 (therefore, corrected by the BrW method). A two- to three-fold difference in prediction values would occur between the two groups only because of choice of animal species. This phenomenon is inevitable and can be considered to be an intrinsic defect associated with use of correction factors or ROE in allometry.

The main purpose of this study was to illustrate the mathematical description of MLP or BrW or ROE correction and to point out the intrinsic defect with use of those correction methods. This intrinsic defect may partially explain the prediction errors made by ROE as noted for many examples (Ward and Smith, 2004;Nagilla and Ward, 2004). However, this is not to say that the ROE method should be discarded. On the contrary, because ROE was proposed based on real observations, it has been applied to many examples and has shown an improved predictability over that of simple allometry. Since there are no other affirmatively proven methods at this time, which can significantly improve the predictability of CL in humans, the empirical ROE method may still serve as an optional approach in predicting human CL.

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Table 1. Values for animal body weights, maximum life-span potential (MLP) and brain weight (BrW)

Species	Body weight (Kg)	MLP (Years)	BrW (Kg)
mouse (m)	0.025	2.758	0.000363
rat (r)	0.333	5.254	0.0025
monkey (k)	5	22.91	0.0660
dog (d)	12	18.39	0.0637
human (h)	70	93.39	1.53

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Table 2. The values for F_{MLP} and F_{BrW} for some common combinations of animal species

Combination of species	F_{MLP}	F_{BrW}
mouse, rat, monkey	0.622	0.474
mouse, rat, dog	0.326	0.172
mouse, monkey, dog	0.455	0.290
rat, monkey, dog	0.505	0.341
mouse, rat, monkey, dog	0.446	0.281