A publication of the American Pharmaceutical Association and the American Chemical Society

JOURNAL OF Pharmaceutical Sciences

November 1999
Volume 88, Number 11

MINIREVIEW

Allometric Issues in Drug Development†

IFTEKHAR MAHMOOD

Contribution from *Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I (HFD-860), Food & Drug Administration, Woodmont Office Center II, Room 4079, 1451 Rockville Pike, Rockville, Maryland 20852.*

Received June 28, 1999. Final revised manuscript received August 5, 1999.
Accepted for publication August 17, 1999.

Abstract ☐ The concept of correlating pharmacokinetic parameters with body weight from different animal species has become a useful tool in drug development. The allometric approach is based on the power function, where the body weight of the species is plotted against the pharmacokinetic parameter(s) of interest. Clearance, volume of distribution, and elimination half-life are the three most frequently extrapolated pharmacokinetic parameters. Over the years, many approaches have been suggested to improve the prediction of these pharmacokinetic parameters in humans from animal data. A literature review indicates that there are different degrees of success with different methods for different drugs. Overall, though interspecies scaling requires refinement and better understanding, the approach has lot of potential during the drug development process.

Introduction

To develop a new therapeutic compound, relevant pharmacological and toxicological studies are initially conducted in small laboratory animals such as mice, rats, rabbits, dogs, or monkeys. These initial studies are helpful in screening the potential therapeutic compounds in the process of drug development. This extrapolation, termed as interspecies scaling, may be helpful in the selection of a suitable dose for first-time administration to humans.

Interspecies scaling is based on the assumption that there are anatomical, physiological, and biochemical similarities between animals.[1,2] Two approaches are generally used for interspecies pharmacokinetic scaling: (i) physiological-based models, and the (ii) allometric method. Though physiological models provide a mechanistic-based evaluation of drug disposition, these models are complex. Many investigators[3−6] have used physiological-based models to predict pharmacokinetic parameters of drugs. Since physiological models are costly, mathematically complex, and time-consuming for their use in drug discovery, and development remains limited.

The anatomical, physiological, and biochemical similarities between animal species can be generalized and expressed mathematically by the allometric equations and have been discussed in detail by Boxenbaum.[7,8] Though the allometric approach is empirical, it is less complicated and easy to use than the physiologically based models. Therefore, this review will only focus on the basic principles, application, and issues of the allometric scaling in pharmacokinetics.

The allometric approach is based on the power function, as the body weight from several species is plotted against the pharmacokinetic parameter of interest. The power function is written as follows:

$$Y = aW^b \tag{1}$$

where Y is the parameter of interest, W is the body weight, and a and b are the coefficient and exponent of the allometric equation, respectively. The log transformation of eq 1 is represented as follows:

$$\log Y = \log a + b \log W \tag{2}$$

where $\log a$ is the y-intercept, and b is the slope.

* Telephone: (301) 594−5575. Fax: (301) 480−3212. e-mail: Mahmoodi@CDER.FDA.GOV.

† The views expressed in this article are those of the author and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

© 1999, American Chemical Society and American Pharmaceutical Association

10.1021/js9902163 CCC: $18.00
Published on Web 09/24/1999

Clearance (CL), volume of distribution (V), and elimination half-life ($t_{1/2}$) are the three most important pharmacokinetic parameters. In the forthcoming sections different allometric approaches to predict these pharmacokinetic parameters from animals to man will be discussed.

Clearance

Both in drug discovery and drug development, clearance is the focus of attention. During drug discovery or the screening process, clearance is important since drugs which are eliminated quickly may have a low bioavailability and may not be suitable for further investigation. Clearance can also play an important role for the selection of the first-time dosing in humans (as inverse of clearance indicates the total exposure (AUC) of a drug). Therefore, over the years, a lot of attention has been focused in order to improve the performance of allometry to predict clearance.

A glance on the literature indicates that clearance cannot be predicted only using the simple allometry (body weight vs clearance).[9,10] Over the years, many different approaches have been suggested to address this issue. Some of the approaches are (i) to predict clearance on the basis of species weight and maximum life-span potential (MLP),[7] (ii) the use of a two-term power equation[11] based on brain weight and body weight to predict intrinsic clearance of drugs, (iii) use of the product of CL × brain weight,[9,10] and (iv) the normalization of in vivo clearance by in vitro clearance versus body weight.[12−14] Unfortunately, these approaches are used indiscriminately without identifying the suitability of a given approach.

In a study, Mahmood and Balian[9] showed that CL × MLP or CL × brain weight estimates the clearance of some antiepileptic drugs more accurately than the simple allometric approach (CL vs body weight). But it is also important to know under what circumstances the simple allometric equation, CL × MLP or CL × brain weight is most suitable. Mahmood and Balian[10] proposed the selection of one of the methods based on the exponents of the simple allometry. The authors demonstrated that there are specific conditions under which only one of the three methods can be used for reasonably accurate prediction (a maximum of 30% error) of clearance: (i) if the exponent of the simple allometry lies between 0.55 and 0.70, simple allometry will predict clearance more accurately than CL × MLP or CL × brain weight; (ii) if the exponent of the simple allometry lies between 0.71 and 1.0, the CL × MLP approach will predict clearance better compared to simple allometry or CL × brain weight; and (iii) if the exponent of the simple allometry is ≥1.0, the product of CL × brain weight is a suitable approach to predict clearance in humans compared to the other two methods. If the exponent of the simple allometry is greater than 1.3, it is possible that the prediction of clearance from animals to man may not be accurate even using the approach of CL × brain weight, and if the exponent of simple allometry is below 0.55, the predicted clearance may be substantially lower than the observed clearance. However, this "rule of exponents" is not rigid, and caution should be applied when the exponents are on the borderline (i.e., 0.69 vs 0.71).

The exponents of allometry have no physiological meaning. As the exponents of the simple allometry get larger, the predicted clearance will be comparatively higher than the observed clearance. Furthermore, the normalization of clearance by MLP or brain weight is a mathematical manipulation which may not be associated with any physiological relevance. The predicted clearance values will be in order of simple allometry > MLP × CL > brain weight × CL. The exponents of a given drug are not universal and will depend on the species used in the allometric scaling. This has been shown for theophylline and antipyrine following iv administration,[10] though this will be true for any given drug.

The concept of using a fixed exponent of 0.75 for the prediction of clearance does not seem to be appropriate. From the data published by Mahmood and Balian,[10] it can be seen that the exponents of allometry range from 0.35 to 1.39. The mean of the exponents is 0.78, which is close to 0.75, but given the wide range of exponents it is obvious that using a fixed exponent of 0.75 will produce serious errors in the prediction of clearance. However, it should be noted that the use of a fixed exponent may be helpful when pharmacokinetic data from only one species are available. This approach may provide a rough estimate of clearance.

Incorporation of in Vitro Data in in Vivo Clearance—Over the years, a lot of interest in using in vitro data in allometric scaling has been developed, and a comprehensive review article has been published by Houston[12] on this topic. Recently, Lave et al.[13] attempted to predict hepatic clearance of 10 extensively metabolized drugs in man by incorporating in vitro data into allometric scaling. The authors concluded that integrating the in vitro data with the allometric approach improved the prediction of clearance in humans as compared to the approach of the simple allometry or the product of clearance and brain weight. In their comparison between simple allometry or the product of clearance and brain weight with the in vitro approach, Lave et al. assumed that clearance of all drugs can be either predicted by simple allometry or by the product of clearance and brain weight. Since this assumption is incorrect, Lave's data[13] were reanalyzed by Mahmood[15] and the results indicated that the normalization of clearance by MLP (as required based on the exponents) could have produced the same results as observed by the in vitro approach. Furthermore, based on the exponents of the simple allometry, it was found that the product of clearance and brain weight was not a suitable approach for the prediction of clearance for these drugs.

In a separate study, Obach et al.[14] used different methods for the prediction of clearance and concluded that the in vitro approach was the best method for the prediction of clearance. In their comparison, the authors also assumed that clearance for all drugs can be predicted by only one method. A comparison between the in vitro approach and the allometry using the "rule of exponents" as suggested by Mahmood and Balian would have provided information whether the in vitro approach is really better than the empirical allometric approach.

There are obvious limitations of the in vitro approach. A definitive disadvantage of the in vitro approach is that one requires to measure the in vitro clearance in at least three species which may be time-consuming. This approach is inappropriate for drugs which are excreted renally as well as for those drugs which are partly metabolized and partly excreted renally.

Extensive work will be needed in this direction before one can clearly establish the advantage and accuracy of the in vitro approach in predicting clearance of drugs over other existing methods. However, it should be kept in mind that the in vitro approach in allometric scaling is one of the many suggested approaches which are attempts to improve the prediction of clearance and should be used as deemed necessary.

Role of Protein Binding in the Prediction of Clearance—Considerable variability in plasma protein binding of drugs have been observed among animal species, resulting in variable distribution and elimination of drugs in different species. The unbound intrinsic clearance of antipyrine,[11] phenytoin,[8] clonazepam,[8] caffeine,[16] and cy-

Table 1—Observed and Total Predicted Clearance (mL/min) of Several Drugs with or without Considering Protein Binding

drug	observed total CL	predicted total CL	predicted total CL
diazepam	26	861	817
tamsulosin	48	814	102
GV150526	5–7	320	5
cyclosporin	273	716	611
quinidine	330	1452	2423

[a] Obtained by multiplying the predicted unbound clearance in humans by free fraction of drug in human plasma. For example, the predicted unbound clearance of tamsulosin in humans was 10218 mL/min and fu was 0.01. Therefore, the predicted total clearance in humans was 10218*0.01 = 102 mL/min.

closporine[17] has been reported in the literature. It is also widely believed that unbound clearance can be predicted with more accuracy than total clearance.[14] However, a systematic study, which compares whether unbound clearance can be predicted better than total clearance, is lacking. Mahmood[18] compared the total and unbound clearance of a wide variety of drugs to determine whether unbound clearance of a drug can be predicted more accurately than total clearance, and if there is any real advantage of predicting unbound clearance. The results of the study indicated that unbound clearance cannot be predicted any better than total clearance. There are drugs whose unbound clearance can be predicted better than total clearance or vice versa. For example, using simple allometry, predicted total clearance of diazepam,[19] tamsulosin,[20] GV 150526,[21] cyclosporin,[17] and quinidine[38–40] was 861, 814, 320, 716, and 1452 mL/min, respectively (Table 1). When the predicted unbound clearance in humans was multiplied by the respective free fraction of drug in human plasma, the predicted total clearances for tamsulosin and GV 150526 were vastly improved, whereas no improvement was observed for diazepam, cyclosporin, and quinidine (Table 1). It is clear from this analysis that protein binding may or may not be helpful for the improved prediction of clearance. At this time it is not possible to determine a priori for which drug unbound or total clearance can be predicted better.

In a separate study, Obach et al.[14] predicted clearance with or without taking protein binding into account. Based on average-fold error (1.91 without protein binding and 1.79 with protein binding), a slightly improved prediction of unbound clearance was noted, though for all practical purposes this difference may not be of any significance.

Prediction of Clearance for Renally Secreted Drugs—Allometry is not always successful in predicting pharmacokinetic parameters. A recent example is the failure of the allometric approach for the prediction of total clearance of renally secreted drugs.[22] Interspecies scaling of drugs for the prediction of clearance may be complicated due to the differences in the mechanism of excretion of drugs in different species. Using 10 renally secreted drugs, it was shown by Mahmood[22] that it is likely that the predicted total and renal clearances for renally secreted drugs may be lower in humans than the observed clearances. The prediction of renal clearance was improved by normalizing the renal clearance by a "correction factor" for animals who exhibited renal secretion. The "correction factor" was obtained by the following equation:

$$\frac{(\text{glomerular filtration rate} \times \text{kidney blood flow})}{(\text{body weight} \times \text{kidney weight})} \quad (3)$$

Though the proposed approach for the prediction of renal clearance for renally secreted drugs worked fairly well on the tested drugs, more work will be needed to validate the approach. Furthermore, a method which can improve the prediction of total clearance for renally secreted drugs requires investigation.

Volume of Distribution—Like clearance, volume of distribution is also an important pharmacokinetic parameter. Volume of distribution of the central compartment (V_c) can play an important role in establishing the safety or toxicity for first-time dosing in humans. Since an administered dose is always known, the predicted V_c can be used to calculate plasma concentration of a drug at time zero (C_0) following intravenous administration. This initial plasma concentration may be an index of safety or toxicity. Furthermore, V_c can also be used to predict half-life, if clearance is known ($t_{1/2} = 0.693V_c/\text{CL}$).

There is a good correlation between body weight and V_c among species. Generally the exponents of volume pivots around 1.0, which indicates that body weight and volume are directly proportional. However, in practice this may not be the case for all drugs; for example, exponents of 0.81, 0.86, 0.58, and 0.76 were observed for topiramate,[9] diazepam,[9] diazepoxide,[23] and ciprofloxacin,[24] respectively. Overall, volume of distribution can be predicted in humans from animals with reasonable accuracy.

Obach et al.[14] used four different methods to predict volume of distribution at steady state (V_{ss}), and on the basis of their geometric mean prediction accuracy they concluded that V_{ss} can be predicted better when protein binding is taken into account.

In the literature one can find that V_{ss} and V_β or V_{area} are also predicted. It has been shown by Mahmood[24] that V_c can be predicted with more accuracy than V_{ss} and V_β. In fact V_{ss} and V_β are of no real significance for the first time dosing in humans and can be estimated from human data.

The concept of a fixed exponent for volume may be acceptable, as in the majority of cases the exponents of volume revolve around 1. Therefore, the use of a fixed exponent of 1 may not produce as much error in predicted volume as clearance and half-life.

Elimination Half-Life—Elimination half-life is difficult to predict across species. Conceptually, it is difficult to establish a relationship between body weight and half-life. In practice, indeed a poor correlation between $t_{1/2}$ and body weight across the species has been found. This poor correlation may be due to the fact that $t_{1/2}$ is not directly related to the physiological function of the body, rather it is a hybrid parameter. Therefore, this poor correlation results in a poor prediction of half-life. To improve the prediction of half-life, some indirect approaches have been suggested by different investigators.

Bachmann,[25] Mahmood and Balian,[9] and Obach et al.[14] used the equation ($t_{1/2} = 0.693V_c/\text{CL}$) to predict the half-lives of many drugs. Though this approach predicted the half-life with reasonable accuracy, to obtain a reasonable prediction of half-life both CL and V_c must be predicted with reasonable accuracy. Another indirect approach was suggested by Mahmood.[24] In this approach, mean residence time (MRT) was predicted, and then predicted MRT was used to predict half-life in humans using the equation ($t_{1/2}$ = MRT/1.44). The results of his study indicated that MRT can be predicted in humans with a fair degree of accuracy from animal data. The predicted half-life from MRT was also reasonably accurate.

Like clearance, the concept of fixed exponent may not be applicable for half-life. From the published work of Mahmood,[24] it can be seen that the exponenmts of half-life varies from −0.066 to 0.547, but the average is 0.19. Therefore, a fixed exponent of 0.25 for the prediction of half-life may also produce serious errors in the prediction of half-life.

Physiological Time or Pharmacokinetic Time Scale—Besides predicting pharmacokinetic parameters, attempts were also made by several investigators to predict plasma concentrations in humans from animal data. The initiative in this direction was taken by Dedrick et al.,[2] and Boxenbaum[7,8] further refined the concept of Dedrick's approach.

In chronological time, heart beat and respiratory rates decrease as the size of the animals increases. On the other hand, on a physiological time scale, all mammals have the same number of heart beats and breaths in their lifetime. The physiological time can be defined as the time required to complete a species independent physiological event. Thus, smaller animals have faster physiological processes and shorter life span. The concept of pharmacokinetic time scale originates from the concept of physiological time which was first described by Brody.[26]

Dedrick et al.[27] were the first to use the concept of physiological time to describe methotrexate disposition in five mammalian species following intravenous administration. They transformed the chronological time to physiological time using the following equation:

$$Y\text{-axis} = \frac{\text{concentration}}{(\text{dose}/W)} \quad (4)$$

$$X\text{-axis} = \frac{\text{time}}{W^{0.25}} \quad (5)$$

where W is the body weight.

By transforming the chronological time to physiological time, the plasma concentrations of methotrexate were superimposable in all species. The authors termed this transformation as "equivalent time". Later, Boxenbaum[7,8] introduced two new units of pharmacokinetic time, kallynochrons and apolysichrons. Kallynochrons and apolysichrons are transformed time units termed as elementry Dedrick plot and complex Dedrick plot, respectively. Boxenbaum also incorporated the concept of MLP in physiological time and termed this new time unit as "dienetichrons".

Though many investigators[28–30] have used the concept of physiological time in their allometric analysis, a direct comparison of allometric approaches with physiological time has not been systematically evaluated. Recently Mahmood and Yuan[31] compared the predicted values of clearance, volume of distribution, and elimination half-life of ethosuximide, cyclosporine, and ciprofloxacine by allometry with physiological time using equivalent time, kallynochron, apolysichron, and dienetichrons. The results of this study indicated that there is no specific advantage of using physiological time over the allometric approach. Almost similar predictions in pharmacokinetic parameters were obtained from both methods. The equivalent time approach based on the assumption that the exponent of half-life is 0.25 was not found to be suitable for the prediction of plasma concentrations or pharmacokinetic parameters. This may be due to the fact that the exponent of elimination half-life of drugs is not always 0.25. Due to the small sample size used in this study, it is difficult to conclude whether the physiological time approach in predicting pharmacokinetic parameters is as good/better as allometric approaches. One advantage of pharmacokinetic time scale approach is that it provides some information about the plasma concentrations of a given drug, though it is not known to what extent the predicted concentrations are reliable?

Prediction of Pharmacokinetic Parameters Using Pharmacokinetic Constants—Swabb and Bonner[32] and Mordenti[33] predicted the plasma concentrations of aztreonam and ceftizoxime, respectively, using an allometric relationship on pharmacokinetic constants (A, B, a, and β). Though the authors successfully used this approach for the prediction of CL, V_c, and $t_{1/2}$, a systematic study of suitability of this approach for prediction of pharmacokinetic parameters was lacking. Mahmood[34] compared the pharmacokinetic parameters of six drugs predicted by pharmacokinetic constants and by the conventional allometric approach.

The following equation representing a two-compartment model following intravenous administration was used to generate plasma concentrations in man from the pharmacokinetic constants predicted from animals.

$$C = Ae^{-\alpha t} + Be-\beta t \quad (6)$$

where A and B are the intercepts on Y-axis of plasma concentration versus time plot. a and β are the rate constants for the distribution and elimination phase, respectively.

Pharmacokinetic constants (A, B, a, and b) were plotted as a function of body weight as described in eq 1. The allometric equation thus generated was used to predict pharmacokinetic constants in man. For the prediction of plasma concentrations in man, the predicted pharmacokinetic constants were used.

The results of the study indicated an inconsistent correlation between body weight and A, B, or a. For some drugs, a good correlation was obtained, whereas a poor correlation was noted for other drugs. Though the prediction of A and B was occasionally reasonable, the predicted a values were manyfold higher or lower than the observed values. Overall it was found that the use of pharmacokinetic constants to predict pharmacokinetic parameters does not necessarily provide an improvement over the conventional allometric approach. Like the pharmacokinetic time scale approach, the pharmacokinetic constant method may provide some information about plasma concentrations of a drug, but the accuracy of the method for the prediction of plasma concentrations in man may not be reliable.

Conclusion

The most important objective of allometric scaling is to select a safe and tolerable dose for the first time administration to humans. Therefore, in recent years, interspecies scaling of pharmacokinetic parameters has drawn enormous attention. Interspecies scaling is not without shortcomings and failures, and over the years, many approaches have been suggested to improve the predictive performance of allometric scaling. These approaches are not perfect, but they may be of considerable importance to understand and refine the concept of allometric scaling. There is no right or wrong approach in interspecies scaling.

There may be anatomical similarities among species, but there are external factors which will affect the allometric scaling. Experimental design, species, analytical errors, and physicochemical properties of drugs such as renal secretion or biliary excretion may have impact on allometric extrapolation. There are drugs such as diazepam,[19] warfarin,[25] valproic acid,[35] tamsulosin,[20] and GV150526[21] whose predicted clearance are manyfold higher than the observed clearance and may be considered as drugs which exhibit vertical allometry. The role and importance of vertical allometry in allometric scaling is unclear. It is also difficult to identify a priori when a drug will exhibit vertical allometry. Extensive work will be needed to classify drugs as vertical allometry and to find a solution to improve the prediction of clearance for such drugs.

There were also attempts to identify the suitability of a particular species for the prediction of clearance in humans. Campbell[36] concluded that the prediction of clearance in humans was best predicted when data from rhesus or cynomolgus monkey were used with the incorporation of MLP. The rat was the next best species for the prediction of human clearance whereas dog appeared to be a poor predictor of clearance in humans. The number of species can also affect the predictive performance of allometry. Mahmood and Balian[37] have shown that three or more species are needed for a reliable prediction of clearance in humans. They also showed that volume of distribution of a compound is predicted equally well using data from two species or more. Therefore, all these methods should be used with caution and proper understanding of allometric scaling.

Besides success, there are numerous failures in interspecies scaling. Such failed studies should also be published so that further investigation can be conducted to find the underlying reasons for failure. Such investigations will be helpful to improve the predictive performance of allometric scaling.

References and Notes

1. Mordenti, J. Man versus beast. *J. Pharm. Sci.* **1986**, *75*, 1028−40.
2. Dedrick, R. L. Animal Scale-up. *J. Pharmacokin. Biopharm.* **1973**, *1*, 435−61.
3. Bischoff, K. B. Some fundamental considerations of the applications of pharmacokinetics to cancer chemotherapy. *Cancer Chemother. Rep.* **1975**, *59*, 777−93.
4. Sugita, O.; Sawada, Y.; Sugiyama. Y.; Iga, T.; Hanano, M. Physiologically based pharmacokinetics of drug-drug interaction: a study of tolbutamide-sulfonamide interaction in rats. *J. Charmacokin. Biopharm.* **1982**, *10*, 297−316.
5. Lin, H.; Sugiyama, Y.; Awazu, S.; Hanano, M. Physiological pharmacokinetics of ethoxybenzamide based on biochemical data obtained in vitro as well as on physiological data. *J. Pharmacokin. Biopharm.* **1982**, *10*, 649−61.
6. King, F. G.; Dedrick, R. L.; Farris, F. F. Physiological pharmacokinetic modeling of cis-dichlorodiammineplatinum (II) (DDP) in several species. *J. Pharmacokin. Biopharm.* **1986**, *14*, 131−55.
7. Boxenbaum, H. Interspecies pharmacokinetic scaling and the evolutionary-comparative paradigm. *Drug. Metab. Rev.* **1984**, *15*, 1071−1121.
8. Boxenbaum, H. Interspecies scaling, allometry, physiological time and the ground plan of pharmacokinetics. *J. Pharmacokin. Biopharm.* **1982**, *10*, 201−27.
9. Mahmood, I.; Balian J. D. Interspecies scaling: Predicting pharmacokinetic parameters of antiepileptic drugs in humans from animals with special emphasis on clearance. *J. Pharm. Sci.* **1996**, *85*, 411−414.
10. Mahmood, I.; Balian J. D. Interspecies scaling: Predicting clearance of drugs in humans. Three different approaches. *Xenobiotica* **1996**, *26*, 887−895.
11. Boxenbaum, H.; Fertig, J. B. Scaling of antipyrine intrinsic clearance of unbound drug in 15 mammalian species. *Eur. J. Drug. Metab. Pharmacokin.* **1984**, *9*, 177−183.
12. Houston, B. Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. *Biochem. Pharmacol.* **1994**, *47*, 1469−1479.13.
13. Lave, T.; Dupin, S.; Schmitt, C.; Chou, R. C.; Jaeck, D.; Coassolo, P. Integration of in vitro data into allometric scaling to predict hepatic metabolic clearance in man: Application to 10 extensively metabolized drugs. *J. Pharm. Sci.* **1997**, *86*, 584−590.
14. Obach, R. S.; Baxter, J. G.; Liston, T. E.; Silber, B. M.; Jones, C.; Macintyre, F.; Rance, D. J.; Wastall, P. The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 46−58.
15. Mahmood, I. Integration of in-vitro data and brain weight in allometric scaling to predict clearance in humans: some suggestions. *J. Pharm. Sci.* **1998**, *87*, 527−529.
16. Bonati, M.; Latini, R.; Tognoni, G. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. *Drug Metab. Rev.* **1984−85**, *15*, 1355−83.
17. Sangalli, L.; Bortollotti, A.; Jiritano, L.; Bonati, M. Cyclosporine pharmacokinetics in rats and interspecies comparison in dogs, rabbits, rats, and humans. *Drug Metab. Dispos.* **1988**, *16*, 749−53.
18. Mahmood, I. Interspecies scaling: A comparative study of unbound vs total clearance. Does unbound clearance improve the predictive performance of allometric scaling? *Pharm. Res.* **1997**, *14*, S-241.
19. Klotz, U.; Antonin, K. H.; Bieck, P. R. Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig and rat. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 67−73.
20. Hoogdalem, E.; Soeish, Y.; Matsushima, H.; Higuchi, S. Disposition of the selective α_{1A}-adrenoceptor antagonist tamsulosin in humans: Comparison with data from interspecies scaling. *J. Pharm. Sci.* **1997**, *86*, 1156−1161.
21. Iavarone, L.; Hoke, J. F.; Bottacini, M.; Barnaby, R.; Preston, G. C. First time in human for GV196771: Interspecies scaling applied on dose selection. *J. Clin. Pharmacol.* **1999**, *39*, 560−566.
22. Mahmood, I. Interspecies scaling of renally secreted drugs. *Life Sci.* **1998**, *63*, 2365−2371.
23. Boxenbaum, H.; Ronfeld, R. Interspecies pharmacokinetic scaling and the Dedrick plots. *Am. J. Physiol.* **1983**, *245*, R768−74.
24. Mahmood, I. Interspecies Scaling: Predicting volumes, mean residence time and elimination half-life. Some suggestions. *J. Pharm. Pharmacol.* **1998**, *50*, 493−499.
25. Bachmann, K. Predicting toxicokinetic parameters in humans from toxicokinetic data acquired from three small mammalian species. *J. Appl. Toxicol.* **1989**, *9*, 331−38.
26. Brody, S. Relativity of physiologic time and physiologic weight. *Growth* **1937**, *1*, 61−67.
27. Dedrick, R. L.; Bischoff, K. B.; Zaharko, D. Z. Interspecies correlation of plasma concentration history of methotrexate (NSC-740). *Cancer Chemother. Rep (Part 1)* **1970**, *54*, 95−101.
28. Hutchaleelaha, A.; Chow, H.; Mayersohn, M. Comparative pharmacokinetics and interspecies scaling of amphotericin B in several mammalian species. *J. Pharm. Pharmacol.* **1997**, *49*, 178−183.
29. Lave, T.; Saner, A.; Coassolo, P.; Brandt, R.; Schmitt-Hoffmann, A. H.; Chou, R. C. Animal pharmacokinetics and interspecies scaling from animals to man of lamifiban, a new platelet aggregation inhibitor. *J. Pharm. Pharmacol.* **1996**, *48*, 573−577.
30. Mehta, S. C.; Lu, D. R.. Interspecies pharmacokinetic scaling of BSH in mice, rats, rabbits, and humans. *Biopharm. Drug. Dispos.* **1995**, *16*, 735−744.
31. Mahmood, I.; Yuan, R. A comparative study of allometric scaling with plasma concentrations predicted by species invariant time methods. *Biopharm. Drug. Dispos.* **1999**, *20*, 137−144.
32. Swab, E.; Bonner, D. Prediction of aztreonam pharmacokinetics in humans based on data from animals. *J. Pharmacokinet. Biopharm.* **1983**, *11*, 215−223.
33. Mordenti, J. Pharmacokinetic scale-up: Accurate prediction of human pharmacokinetic profiles from human data. *J. Pharm. Sci.* **1985**, *74*, 1097−1099.
34. Mahmood, I. Prediction of clearance, volume of distribution and half-life by allometric scaling and by plasma concentrations predicted by pharmacokinetic constants: A comparative study. *J. Pharm. Pharmacol.* **1999**, *51*, 905−910.
35. Loscher, W. Serum protein binding and pharmacokinetics of valproate in man, dog, rat and mouse. *J. Pharmacol. Exp. Ther.* **1978**, *204*, 255−261.

36. Campbell, B. D. Can allometric interspecies scaling be used to predict human kinetics? *Drug. Inform. J.* **1994**, *28*, 235−45.
37. Mahmood, I.; Balian J. D. Interspecies scaling: a comparative study for the prediction of clearance and volume using two or more than two species. *Life Sci.* **1996**, *59*, 579−85.
38. Guentert, T. W.; Huang, J. D.; Qie, S. Disposition of quinidine in the rabbit. *J. Pharm. Sci.* **1982**, *71*, 812−815.
39. Ueda, C. T.; Ballard, B. E.; Rowland, M. Concentration−time effects on quinidine disposition kinetics in rhesus monkeys. *J. Pharmacol. Exp. Ther.* **1977**, *200*, 459−468.
40. Swada, Y.; Hanano, M.; Sugiyama, Y., Iga, T. Prediction of the disposition of nine weakly acidic and six weakly basic drugs in humans from pharmacokinetic parameters in rats. *J. Pharmacokin. Biopharm.* **1985**, *13*, 477−492.

JS9902163