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The Pharmacokinetic Principles Behind Scaling from Preclinical Results to Phase I Protocols

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Abstract

Extrapolation of animal data to assess pharmacokinetic parameters in humans is an important tool in drug development. Allometric scaling has many proponents, and many different approaches and techniques have been proposed to optimise the prediction of pharmacokinetic parameters from animals to humans. The allometric approach is based on the power function $Y = aW^b$, where the bodyweight of the species is plotted against the pharmacokinetic parameter of interest on a log-log scale. Clearance, volume of distribution and elimination half-life are the 3 most frequently extrapolated pharmacokinetic parameters.

Clearance is not predicted very well (error between predicted and observed clearance >30%) using the basic allometric equation in most cases. Thus, several other approaches have been proposed. An early approach was the concept of neoteny, where the clearance is predicted on the basis of species bodyweight and maximum life-span potential. A second approach uses a 2-term power equation based on brain and bodyweight to predict the intrinsic clearance of drugs that are primarily eliminated by phase I oxidative metabolism. Most recently, the use of the product of brain weight and clearance has been proposed. A literature review reveals different degrees of success of improved prediction with the different methods for various drugs. In a comparative study, the determining factor in selecting a method for prediction of clearance was found to be the value of the exponent. Integration of *in vitro* data into *in vivo* clearance to improve the predictive performance of clearance has also been suggested. Although there are proponents of using body surface area instead of bodyweight, no advantage has been noted in this approach. It has also been noted that the unbound clearance of a drug cannot be predicted any better than the total body clearance (CL).

In general, there is a good correlation between bodyweight and volume of the central compartment (V_c); hence, V_c does not face the same complications as CL.

The relationship between elimination half-life ($t_{1/2}\beta$) and bodyweight across species results in poor correlation, most probably because of the hybrid nature of this parameter. When a reasonable prediction of CL and V_c is made, $t_{1/2}\beta$ may be predicted from the equation $t_{1/2}\beta = 0.693V_c/CL$.

The new drug research and development process involves the study of potential therapeutic compounds in small laboratory animals such as in mice, rats, rabbits, dogs or monkeys. For ethical

reasons, relevant pharmacological and toxicological studies of compounds are conducted in animals before being administered to humans. Data obtained in animals can be of considerable importance in the process of drug development, and pharmacokinetics is the vital link in the prediction of pharmacokinetic parameters in humans. This extrapolation, termed as interspecies scaling, may be helpful in facilitating the process of the transition of dosage regimens from animals to humans and accelerating the drug testing process.

Interspecies scaling is based on the assumption of anatomical, physiological and biochemical similarities between animal species.[1,2] Interspecies pharmacokinetic scaling can be performed using 2 approaches: (i) physiological-based models; and (ii) an empirical allometric method. Physiological models provide a mechanistic-based evaluation of drug disposition. These models require organ size, organ blood flow rates, tissue to blood partitioning and metabolic chemical reaction rates. Plasma protein binding, enzymatic kinetic parameters and *in vitro* and *in vivo* clearance data may also be incorporated in a physiologically-based interspecies scaling. This approach has been used by many investigators[3-6] to predict the kinetic behaviour of drugs. Physiological models, however, have been found to be of only limited use in drug discovery and development because this approach is costly, mathematically complex and time consuming.

The anatomical, physiological and biochemical similarities between animal species can be generalised and expressed mathematically by allometric equation(s) and have been discussed in detail by Boxenbaum.[7-8] Although the allometric approach is empirical, it is less complicated and easier to use than the physiologically-based method. The focus of this brief article is to review the basic principles and application of the allometric scaling methods in pharmacokinetics.

The allometric approach has been based on the power function, as the bodyweight (or surface area) from several species is plotted against the pharmacokinetic parameter of interest on a log-log scale. The power function is written as follows:

$$Y = aW^b \quad \text{(Eq. 1)}$$

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

$$\log Y = \log a + b \log W \quad \text{(Eq. 2)}$$

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

Total body clearance (CL), volume of distribution of the central compartment (V_c) and elimination half-life ($t_{½\beta}$) are the 3 most important pharmacokinetic parameters for the allometric approach. The following sections describe the different allometric approaches used to extrapolate these parameters from animals to humans.

1. Total Body Clearance

Organ clearance (CL_o) is a function of organ blood flow ($\dot{Q}$) and the extraction ratio (E) [the capacity of the organ to remove drug as blood perfuses through the organ].

$$CL_o = \dot{Q}E \quad \text{(Eq. 3)}$$

Intrinsic clearance (CL_{int}) is described as the ability of the liver to remove drug in the absence of flow limitations. Hepatic clearance (CL_H) is related to both liver blood flow and the intrinsic clearance of the liver.

$$CL_H = \dot{Q}\left[\frac{CL_{int}}{\dot{Q} + CL_{int}}\right] \quad \text{(Eq. 4)}$$

The relationship of blood flow, intrinsic clearance and protein binding can be described as:

$$CL_H = \dot{Q}\left[\frac{f_u CL'_{int}}{\dot{Q} + f_u CL'_{int}}\right] \quad \text{(Eq. 5)}$$

where f_u is the fraction of drug unbound in blood and CL'_{int} is unbound intrinsic clearance. When the product of $f_u \times CL'_{int}$ is very small compared with the hepatic blood flow, then equation 5 can be described as:

$$CL_H = f_u CL'_{int} = CL_{int} \quad \text{(Eq. 6)}$$

When $f_u \times CL'_{int}$ are very large compared with hepatic blood flow, then equation 5 can be described as:

$$CL_H = \dot{Q} \quad \text{(Eq. 7)}$$

Therefore, for drugs with a very high CL_{int}, CL_H will depend on hepatic blood flow.

Total systemic clearance is the sum of all clearances occurring from individual processes. The liver and kidneys are the 2 major organs for clearing drugs from the body. If the minor contribution of other organs are ignored then the systemic clearance can be given by the sum of CL_H and renal clearance (CL_R).

$$CL = CL_H + CL_R \quad \text{(Eq. 8)}$$

CL, CL_H and CL_R can be correlated with bodyweight. If a drug is extensively metabolised or excreted extensively by the kidneys, then CL will be equal to CL_H or CL_R, respectively.

1.1 Mean Life-Span Potential

A survey of the literature[9] indicated that drug clearance could not be predicted very well (within 30% of actual values) just using equation 1. Over the years many theories and different approaches have been proposed to improve the predictive performance of allometry for clearance. One such approach is based upon the concept of neoteny[7] where the clearance is predicted on the basis of species bodyweight and maximum life-span potential (MLP)

$$CL = \frac{a(MLP \times Clearance)^b}{8.18 \times 10^5} \quad \text{(Eq. 9)}$$

where 8.18×10^5 (in hours) is the MLP value in humans, and a and b are the coefficient and the exponent of the allometric equation, respectively.

MLP in years was calculated from the following equation as described by Sacher:[10]

$$MLP\ (years) = 185.4(BW)^{0.636}(W)^{-0.225} \quad \text{(Eq. 10)}$$

where both brain weight (BW) and bodyweight (W) are in kilograms.

Another approach suggested by Boxenbaum and Fertig[11] used a 2-term power equation based on brain weight and bodyweight to predict the intrinsic clearance of drugs which were primarily eliminated by phase I oxidative metabolism. In their approach, Boxenbaum and Fertig[11] predicted the intrinsic clearance of phenazone (antipyrine) in 15 mammalian species using the following equation:

$$CL_{u,int} = X(W)^a(BW)^b \quad \text{(Eq. 11)}$$

where X is the coefficient and a and b are the exponents of the allometric equation.

Using the product of brain weight and clearance, Mahmood and Balian[12,13] attempted to improve the predictive performance of allometric scaling for clearance. In this approach the clearance in animals was multiplied by the brain weight of the species and the product ($CL \times BW$) was plotted as a function of bodyweight on a log-log scale. The allometric equation (equation 12) was used to predict the clearance of a given drug in humans using the human brain weight (1.53kg):

$$CL \times BW = aW^b \quad \text{(Eq. 12)}$$

Mahmood and Balian[12] evaluated 4 methods to predict the clearance of 7 anticonvulsant drugs in humans from data obtained from at least 3 animal species. The 4 methods utilised were the simple allometric approach (eq. 1), the MLP approach (eq. 9), Boxenbaum's 2-term power equation (eq. 11) and a new empirical approach proposed by the authors (eq. 12).

From that study, the authors concluded that all of the above mentioned methods could predict clearance with different degrees of accuracy.

As a follow-up of their previous study, Mahmood and Balian[13] evaluated 3 methods to predict the clearance of 40 drugs in humans from data obtained from at least 3 animal species. The 3 methods utilised were the simple allometric approach (eq. 1), the MLP approach (eq. 9) and the new empirical approach proposed by them (eq. 12). From that study, they concluded that the determining factor in selecting a method for prediction of clear-

Table I. Predicted versus observed clearance (L/h) of some drugs in humans using bodyweight or body surface area

Drug	Observed clearance	Bodyweight		Body surface area		Reference
		exponent	predicted clearance	exponent	predicted clearance	
Acivicin	2.9	0.595	3.06	0.890	3.0	19
Amsacrine	21.1	0.422	13.8	0.631	12.6	20
Cisplatin	6.0	1.002	23.2	1.521	23.5	6
Cyclophosphamide	12.0	0.863	37.6	1.307	37.5	7
Cyclosporin	16.4	1.146	43.1	1.733	42.8	21
Cytarabine	5.4	0.830	8.6	1.236	8.4	22
Diazepam	1.6	0.737	51.7	1.120	52.0	23
Erythromycin	29.5	0.807	86.7	1.220	86.2	24
Ethosuximide	0.7	0.509	0.6	0.771	0.6	25
Methotrexate	8.8	0.645	9.4	0.977	9.3	7
Oleandomycin	38.2	0.664	28.9	1.007	28.9	24
Valproic acid (sodium valproate)	0.5-0.8	0.950	12.5	1.427	11.8	26

ance was the value of the exponent: for exponents between 0.55 to 0.70 the simple allometric equation was suitable for the prediction of clearance; for exponents between 0.71 to 1.0 the simple allometric equation substantially overestimated the clearance value and the MLP method was a suitable approach; and, for exponents >1.0 both the simple allometric and the MLP equations substantially overestimated the clearance value and the product of clearance and brain weight predicted clearance more accurately than the other 2 methods.

1.2 Incorporation of *In Vitro* Data in *In Vivo* Clearance

There is a great deal of interest in using *in vitro* data in allometric scaling and an excellent review article has been published by Houston[14] on this topic. In a recent study, Lave et al.[15] investigated *in vitro* data of allometric scaling to predict hepatic clearance in humans of 10 extensively metabolised drugs. These authors evaluated several methods to predict the clearance of 10 drugs that were mainly eliminated through hepatic metabolism. In their approach, they determined the rate of metabolism of these drugs with various animal species and human liver microsomes and hepatocytes. Using the *in vitro* metabolism data and combining it with the *in vivo* data from animals, they predicted the *in vivo* clearance in humans using allometric scaling techniques. Their conclusion was that integrating the *in vitro* data with the allometric approach with data obtained from at least 3 animal species improved the predictions of human clearance when compared with the approach of direct extrapolations made from bodyweight.

1.3 Body Surface Area (bsa)

It has been suggested[16,17] that in allometric scaling the use of body surface area (bsa) in place of bodyweight would improve the prediction of clearance in humans. The clearance of 9 anticancer drugs were compared using bodyweight and body surface area.[18] The body surface area of the animals was calculated as described by Chappel and Mordenti[16]

$$\text{bsa } (m^2) = 1.85(W/70)^{2/3} \quad \text{(Eq. 13)}$$

where W is bodyweight in kg.

Table I compares the clearance of drugs using body surface area and bodyweight. The results of the allometric scaling using body surface area were not different from the results obtained using bodyweight. Therefore, it appears that there is no real advantage using body surface area over bodyweight for the prediction of clearance of drugs.

1.4 Number of Species in Allometric Scaling

Interspecies scaling to predict pharmacokinetic parameters in humans is generally performed on data obtained from at least 3 animal species. It is presumed that the greater the number of species used the better the chances of accurate predictions of pharmacokinetic parameters. However, testing more species adds to the time and cost of drug development. In the past, some investigators have used 2 species to predict pharmacokinetic parameters in humans. Boxenbaum[27] used dog and human data from 12 benzodiazepines in an attempt to predict clearance in humans.

Sawada et al.[28] predicted the disposition of various acidic and basic drugs in humans based on data from rats alone. Chiou and Hsu[29] used rat and human data to correlate unbound clearance values of 15 highly metabolised drugs. Mahmood and Balian[30] conducted a study to determine whether a 2 species model could predict clearance and volume of distribution (Vd) in humans as accurately as predictions obtained by using 3 or more species (excluding humans).

Based on the evaluation of 12 compounds the authors concluded that: (i) 3 or more species are needed for a reliable prediction of clearance; and (ii) the Vd of a compound is predicted equally well using data from 2 or more species.

1.5 Protein Binding

The plasma protein binding of drugs varies considerably among animal species. As a result, the distribution and elimination of drugs may be variable in different species. Over the span of many years, several attempts were made by investigators to predict the unbound clearance of drugs. The unbound intrinsic clearance of phenazone,[11] phenytoin,[8] clonazepam,[8] caffeine[31] and cyclosporin,[21] with or without normalisation to MLP, has been reported in the literature. However, there have been no systematic allometric studies comparing the predictive performance of unbound clearance versus total clearance.

Using the simple allometric or the MLP approach, Mahmood[32] compared the total and unbound clearance of a wide variety of drugs to determine whether the unbound clearance of a drug could be predicted more accurately than total clearance, and if there was any real advantage in predicting unbound clearance. Table II compares the total body clearance and unbound clearance of several drugs predicted by simple allometry. The results of the study indicated that, whether a drug is excreted renally or by extensive metabolism, unbound clearance could not be predicted any better than total body clearance. Furthermore, scaling based on unbound clearance may become expen-

Table II. Observed versus predicted total clearance (CL) and unbound clearance (CL_u)[a] (L/h) in humans

Drug	CL		CL_u		Reference
	observed	predicted	observed	predicted	
Cefmetazole	6.7	10.4	44.7	30.5	33
Cefoperazone	4.3	4.6	24.1	19.9	33
Cyclosporin	16.4	43.0	252.0	523.8	21
Diazepam	1.6	51.7	46.8	1531.5	23
Enprofylline	18.9	3.0	38.7	16.6	34
Latamoxef (moxalactam)	4.9	4.4	12.4	9.1	33
Propranolol	51.0	43.0	750.0	4750.2	35
Remoxipride	7.1	9.9	35.5	108.7	36,37
Theophylline	3.3	6.8	5.6	9.1	38
Valproic acid (sodium valproate)	0.7	12.2	13.2	76.4	26

a The unbound clearance was estimated as follows: $CL_u = CL/f_u$, where f_u represents the free fraction of drug in plasma. Total and unbound clearance was predicted using following equation: CL or $CL_u = aW^b$, where a is the coefficient of the allometric equation, W is bodyweight and b is the exponent of the allometric equation.

sive and time consuming if one has to obtain protein binding data in animals for scaling purposes.

1.6 Vertical Allometry

In an allometric plot of anthropoid primate brain weight against bodyweight, human brain weight was predicted to be almost 3.5-fold smaller than the measured brain weight (predicted = 0.45kg, observed = 1.53kg).[39] This phenomenon may be due to a special capability of adaptation and was termed as vertical allometry by Calder.[40] Many drugs also exhibit vertical allometry. Vertical allometry has been reported for diazepam. The predicted clearance of diazepam in humans (51.7 L/h) is 33-fold greater than the observed clearance (1.56 L/h). Besides diazepam, drugs like warfarin (predicted = 2.64 L/h, observed = 0.24 L/h) and valproic acid (sodium valproate) [predicted = 12.48 L/h, observed = 0.48 to 0.78 L/h] may be considered as drugs which follow vertical allometry.

There are many unanswered questions regarding vertical allometry. What is the role and importance of vertical allometry in allometric scaling? In the absence of human data, how could one identify which drug will follow vertical allometry? If somehow one could identify vertical allometry from animal data, how could this information be used to make a reasonable prediction of clearance in humans? How much difference should there be between predicted and observed values before a drug could be declared to follow vertical allometry? To be categorised as having vertical allometry should the observed clearance in humans always be less than the predicted clearance? Based on the suggestions of Mahmood and Balian,[13] it appears that the exponents of simple allometric scaling (clearance *vs* bodyweight) could be used to identify vertical allometry. However, depending on the species and number of species, the value of the exponent could be changed.

For example, when the clearance of theophylline was scaled from mice, rats, rabbits and dogs,[38,41] the clearance was predicted accurately by a simple allometric equation (exponent = 0.66, r = 0.954). The predicted clearance of theophylline was 2.52 L/h, whereas the observed clearance was 2.76 L/h. Using the clearance data from rats, rabbits and dogs, the predicted clearance of theophylline was 5.88 L/h (the exponent from the simple allometric equation was 0.92, r = 0.99). Under these circumstances, could theophylline be categorised as a drug which follows vertical allometry? It appears that extensive work will be needed before a conclusive classification of drugs will be possible based on vertical allometry. The concept of vertical allometry at this time appears complex and obscure but in coming years may prove a useful tool in allometric scaling.

2. Volume of Distribution

The Vd of the central compartment (V_c) is used to relate plasma concentration at time zero (C_0) of a drug and the amount of drug (X) in the body.

$$X = V_c \times C_0 \quad \text{(Eq. 14)}$$

The following 2 volume terms are also frequently used. The Vd at steady state (V_{ss}) can be estimated from the following equation:

$$V_{ss} = CL \bullet MRT \quad \text{(Eq. 15)}$$

where MRT is the mean residence time (AUMC/AUC), AUMC is the area under the moment concentration-time curve and AUC is the area under the drug plasma concentration-time curve.

The Vd by area (V_{area}), also known as V_β, can be obtained from the following equation:

$$V_\beta = \text{Clearance}/\beta \quad \text{(Eq. 16)}$$

where β is the elimination rate constant.

Generally the Vd correlates well with bodyweight. A good prediction of volume will be obtained if the volume is proportional to bodyweight (i.e. $W^{1.0}$). However, this is not the case for all drugs; for example, exponents of 0.81, 0.86, and 0.58 were observed for topiramate,[12] diazepam[12] and diazepoxide,[42] respectively.

Several studies have been conducted to establish the relationship between binding to plasma proteins and the Vd of many drugs in animals and humans. Sawada et al.[33] investigated the relation-

ship between the Vd and plasma protein binding of β-lactam antibactrials. Sawada et al.[28] also investigated the relationship between the unbound volume of distribution of tissues (V_t/f_{ut}) and the unbound fraction (f_u) of 10 weak basic drugs. The authors concluded that there was little difference in V_t/f_{ut} of the basic drugs between animals and humans and that volume in humans from animal data was predicted with more accuracy using V_t/f_{ut} than using volume against f_u.

3. Elimination Half-Life

Predicting clearance alone may not be enough in establishing a first time dosage administration scheme in humans. $t_{½\beta}$ and V_c also play an important role in this direction. In the 1-compartment model, $t_{½\beta}$ can be related to volume and clearance by the following equation:

$$t_{½\beta} = \frac{0.693V}{CL} \quad \text{(Eq. 17)}$$

In practice, the relationship between $t_{½\beta}$ and bodyweight across the species resulted in a poor correlation, and hence the predicted $t_{½\beta}$ was in gross error.[9] This poor correlation may have been due to the fact that $t_{½\beta}$ is a hybrid parameter, i.e. not directly related to the physiological function of the body.[9]

Mahmood and Balian[12] compared the predictive performance of $t_{½\beta}$ with equation 17 and simple allometry (bodyweight *vs* $t_{½\beta}$). The results indicated that $t_{½\beta}$ could be predicted more accurately from equation 17 than simple allometry, provided reasonably accurate estimates of CL and V_c were obtained by allometry. Though equation 17 is only true for the 1-compartment model, the authors showed that equation 17 could also be used for the 2-compartment model for prediction purposes.

4. Species Invariant Time Methods

In chronological time, as animal size increases, heart and respiratory rates decrease. However, on a physiological time scale, regardless of their size 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, in smaller animals the physiological processes are faster and the life-span is shorter.

The physiological time can be obtained by transforming chronological time into a species invariant time. Dedrick et al.[43] were the first to apply the concept of species invariant time to methotrexate disposition in 5 mammalian species following intravenous administration. The transformation of chronological time to physiological time was achieved as follows:

$$\text{Y-axis} = \frac{\text{Concentration}}{\text{Dose/W}} \quad \text{(Eq. 18)}$$

$$\text{X-axis} = \frac{\text{Time}}{W^{0.25}} \quad \text{(Eq. 19)}$$

where W is the bodyweight.

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] refined the concept of equivalent time by introducing 2 new units of pharmacokinetic time, kallynochrons and apolysichrons. Kallynochrons and apolysichrons are transformed time units in elementary and complex Dedrick plots, respectively.

Kallynochrons (elementary Dedrick plot):

$$\text{Y-axis} = \frac{\text{Concentration}}{\text{Dose/W}} \quad \text{(Eq. 20)}$$

$$\text{X-axis} = \frac{\text{Time}}{W^{1-b}} \quad \text{(Eq. 21)}$$

where b is the exponent of clearance.

Apolysichrons (complex Dedrick plot):

$$\text{Y-axis} = \frac{\text{Concentration}}{\text{Dose/W}^c} \quad \text{(Eq. 22)}$$

$$\text{X-axis} = \frac{\text{Time}}{W^{c-b}} \quad \text{(Eq. 23)}$$

where b and c are the exponents of clearance and volume, respectively.

Dienetichrons:

Boxenbaum also incorporated the concept of MLP in physiological time and termed this new time unit as dienetichrons. The transformation of chronological time to dienetichrons was obtained by dividing the X-axis or time by MLP. For example, for the elementary Dedrick plot, the X-axis or time was normalised as follows:

$$\text{X-axis} = \frac{\text{Time}}{\text{MLP}} \bullet \frac{1}{W^{1-b}} \qquad \text{(Eq. 24)}$$

Though many investigators[44-46] have used the concept of species invariant time in their allometric analysis, a direct comparison of allometric approaches with species invariant time has not been systematically evaluated. Further work is needed in this direction to evaluate if there is any real advantage of the species invariant approach over the simple allometric method.

5. Discussion

In recent years, the interspecies scaling of pharmacokinetic parameters (CL, Vd and $t_{½\beta}$) has gained enormous attention, mainly for purposes of designing safe dosage regimens for first time administration to humans. Interspecies scaling is not without controversies and shortcomings, and over the years, considerable efforts have been put forth to improve the predictive performance of allometric scaling. Among numerous approaches (scaling based on physiological models, species-invariant time methods and the simple allometric approach), it appears that physiological models are expensive, time consuming and mathematically complex. Species-invariant time methods have not yet been systematically tested, and therefore it is not known whether this approach has any advantage over simple allometric scaling. This leaves the simple allometric approach as an attractive option to provide reliable predictions of the above-mentioned pharmacokinetic parameters at a low cost and in less time.

CL is an important pharmacokinetic parameter and results presented herein find that the CL of a drug cannot be consistently predicted using simple allometry alone. Normalisation of clearance by brain weight, though in different mathematical ways (in MLP, 2-term power function and product of clearance and brain weight), has been proposed to improve the prediction by Boxenbaum (MLP and 2-term power equation)[7,11] and Mahmood and Balian (product of clearance and brain weight).[12,13]

As suggested by Mahmood and Balian,[13] based on the exponents of allometric scaling, one can use MLP or product of the brain weight and clearance to improve the prediction of clearance. It should be noted that the rules of exponents as suggested by Mahmood and Balian are by no means rigid and there will be exceptions.[13] This approach is not perfect but it certainly provides a rationale for the use of one of the allometric methods which may be most suitable for the prediction of clearance.

Boxenbaum and Dilea[47] mentioned that neoteny was a trivial biological phenomena with no real relationship to the phase I oxidative metabolism of drugs. However, the authors of this review noted that MLP was a useful tool that could be used to predict both the total and intrinsic clearance of drugs.[12]

A re-analysis of the data from Lave et al.[15] indicated that the normalisation of clearance by MLP (as required based on the exponents) could have produced the same results as seen when *in vitro* clearance was incorporated in *in vivo* clearance.[48] However, this method has yet to be proven superior to any other existing method. Mahmood and Balian's proposal[13] seems to work fairly well on the data presented by Lave et al.[15] As described earlier (section 1.1), in order to predict clearance using MLP, the exponent of simple allometric equation should be between 0.7 to 1. Out of 10 drugs evaluated by Lave et al., 7 drugs met the criteria where MLP was applicable (exponent $> 0.7 < 1$).

In a separate study, Obach et al.[49], using 12 different methods, concluded that the *in vitro* approach was the best method for the prediction of clearance. On average, the predicted clearance was within 70 to 80% of the actual values. Extensive work will be needed in this direction before one can clearly establish the advantage and accuracy of the

Table III. Observed versus predicted volume of distribution of central compartment (V_c), volume of distribution at steady state (V_{ss}) and volume of distribution by area (V_β). V_c, V_{ss} and V_β were calculated according to equations 14, 15 and 16, respectively

Drug	V_c (L)			V_{ss} (L)			V_β (L)			References
	observed	predicted	error (%)	observed	predicted	error (%)	observed	predicted	error (%)	
Cefpiramide	4	5	25	8	8	0	8	9	13	50,51
Ciprofloxacin	31	39	26	122	222	82	157	194	87	52-55
Cyclosporin	25	26	4	91	160	76	147	276	88	21
Erythromycin	55	91	65	62	195	215	93	233	151	24
Remoxipride	45	35	22	49	108	120	50	93	86	36,37
Tolcapone	5	7	40	9	13	44	13	22	69	56

in vitro approach in predicting drug clearance over other existing methods.

The limitations of the *in vitro* approach should be kept in mind. A definite disadvantage is the necessity of measuring *in vitro* clearance. Furthermore, this approach would obviously be inappropriate for drugs excreted renally. It is also not known how well this approach would predict drug clearance if a drug was partly metabolised and partly excreted renally. Therefore, any interpretation of the *in vitro* approach requires caution and sound scientific judgement.

Protein binding does not seem to have an effect on the predictive performance of allometric scaling for clearance. As seen in table II, there is no real advantage of measuring unbound clearance over total clearance. Likewise, using body surface area in place of bodyweight did not improve the prediction of clearance of studied drugs (table I).

Like clearance, the V_c is also an important pharmacokinetic parameter. Since the administered dose is always known, based on the knowledge of V_c, one can calculate the plasma concentration of a drug at time zero following intravenous administration. This initial plasma concentration may play an important role in establishing the safety or toxicity for administration of drugs for the first time in humans. Attempts have also been made to predict V_{ss} and V_β. It should be noted that both V_{ss} and V_β may not be predicted as accurately as V_c (table III). Furthermore, V_{ss} and V_β are of no real significance for first time administration in humans and can be estimated from human data.[49]

$t_{½\beta}$ is difficult to predict across species. The prediction of $t_{½\beta}$ based on the equation $CL = V_c\beta$, has been investigated by Bachmann,[41] Mahmood and Balian,[12] and Obach et al.[49] This approach predicted $t_{½\beta}$ with reasonable accuracy but it should be kept in mind that in order to obtain a reasonable prediction of $t_{½\beta}$, both CL and V_c must be predicted with reasonable accuracy. Another approach which could be used would be to first predict MRT; from the predicted MRT, attempts could be made to predict $t_{½\beta}$ in humans. This approach has been studied by Mahmood,[57] and the findings of his study indicated that one could predict MRT in humans with a fair degree of accuracy from animal data. Furthermore, the predicted MRT could be used for the prediction of $t_{½\beta}$.

Scaling can be species dependent. Like theophylline, ethosuximide also provides interesting observations. When the clearance of ethosuximide was scaled from mice, rat and dog,[25] the clearance was predicted accurately by a simple allometric equation (exponent = 0.51, r = 0.880). The predicted clearance of ethosuximide was 0.6 L/h, whereas the observed clearance was 0.72 L/h. Using the clearance data from rat, rabbit and dog,[41] the exponent of simple allometry was 1.01 (r = 0.953). The predicted clearance using simple allometry, MLP and the product of brain weight and clearance was 2.64, 0.9 and 0.6 L/h, respectively. It is the experience of the authors that one would observe this kind of phenomena regularly in interspecies scaling.

Campbell[58] investigated the suitability of a particular species for the prediction of clearance in

humans. The author reported that the prediction of clearance in humans was best predicted when data from rhesus or cynomolgus monkey were used with a correction for MLP. The rat was the next best species for the prediction of human clearance whereas dogs appeared to be poor predictors. Based on limited data analysis, the authors noted that pigs also may be poor predictors of clearance in humans, especially when MLP is incorporated in the scaling.

6. Conclusions

In summary, this review of the literature on interspecies scaling has revealed an evolving science with the potential for a more efficient drug development process. It appears that interspecies scaling can be a useful tool to predict some pharmacokinetic parameters to assist in the design of a well tolerated dosage regimen for first time dosage administration to humans. This review has considered the many approaches and methodologies of interspecies scaling; importantly, it should be emphasised that there is no right or wrong approach in interspecies scaling.

Allometric extrapolation is affected by experimental design, species (as seen with theophylline and ethosuximide), analytical errors, variation from one laboratory to another, in actual parameters measured and the bodyweight range of the species under study. Therefore, all these methods should be used with caution and a proper understanding of allometric scaling. It should also be noted that the use of human data as one of the species to predict pharmacokinetic parameters in humans defeats the purpose of allometric scaling. Efforts are continuing in an attempt to understand more about interspecies scaling, and at the same time, minimise shortcomings associated with its use.

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