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Interspecies Scaling: Predicting Volumes, Mean Residence Time and Elimination Half-life.* Some Suggestions

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Abstract

Extrapolation of animal data to assess pharmacokinetic parameters in man is an important tool in drug development. Clearance, volume of distribution and elimination half-life are the three most frequently extrapolated pharmacokinetic parameters. Extensive work has been done to improve the predictive performance of allometric scaling for clearance. In general there is good correlation between body weight and volume, hence volume in man can be predicted with reasonable accuracy from animal data. Besides the volume of distribution in the central compartment (V_c), two other volume terms, the volume of distribution by area (V_β) and the volume of distribution at steady state (Vd_{SS}), are also extrapolated from animals to man. This report compares the predictive performance of allometric scaling for V_c, V_β and Vd_{SS} in man from animal data.

The relationship between elimination half-life (t½) and body weight across species results in poor correlation, most probably because of the hybrid nature of this parameter. To predict half-life in man from animal data, an indirect method (CL = VK, where CL = clearance, V is volume and K is elimination rate constant) has been proposed. This report proposes another indirect method which uses the mean residence time (MRT). After establishing that MRT can be predicted across species, it was used to predict half-life using the equation $MRT = 1{\cdot}44 \times t½$.

The results of the study indicate that V_c is predicted more accurately than V_β and Vd_{SS} in man. It should be emphasized that for first-time dosing in man, V_c is a more important pharmacokinetic parameter than V_β or Vd_{SS}. Furthermore, MRT can be predicted reasonably well for man and can be used for prediction of half-life.

Small laboratory animals such as mice, rats, rabbits, dogs and monkeys are widely used for research and development of new drugs. To assess safety and toxicity in man, animal studies can be reasonably extrapolated to man by use of pharmacokinetic principles. Prediction of pharmacokinetic parameters in man from data obtained in animals can be of considerable importance in the process of drug development. Such extrapolations are known as interspecies scaling and are based on the assumption of anatomical, physiological and biochemical similarities between animal species (Boxenbaum 1982, 1984). The anatomical, physiological, and biochemical similarities between animal species can be generalized and expressed mathematically by the allometric equation(s) and have been discussed in detail (Boxenbaum 1982, 1984). The allometric approach has been based on the power function, because the body weight of several species is plotted against the pharmacokinetic parameter of interest on a log–log scale. The power function is written:

$$Y = aW^b \quad (1)$$

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 equation 1 is:

$$\log Y = \log a + b \log W \quad (2)$$

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

Clearance (CL), volume of distribution of the central compartment (V_c), and elimination half-life (t½) are the three most important pharmacokinetic

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parameters. Many theories and different approaches have been proposed for improving the predictive performance of allometry for clearance. Normalization of clearance by mean lifespan potential (Boxenbaum 1984), by use of a two-term power equation (Boxenbaum & Fertig 1984), the product of clearance and brain weight (Mahmood & Balian 1996a, b) and incorporation of in-vitro data in in-vivo clearance (Houston 1994; Lave et al 1997) have been suggested by many investigators.

Generally, volume of distribution correlates well with body weight. A good prediction of volume will be obtained if the volume is proportional to body weight, for instance $W^{1.0}$. The volume of distribution of the central compartment (V_c) is used to relate plasma concentration of a drug at time zero (C_0) to the amount of drug in the body (X) (Shargel & Yu 1993).

$$X = V_c \times C_0 \quad (3)$$

Besides V_c, two other volume terms are also frequently estimated. The volume of distribution by area (V_{area}), also known as V_β, can be obtained from the equation (Shargel & Yu 1993):

$$V_\beta = \text{Clearance}/\beta \quad (4)$$

where β is the elimination rate constant.

The volume of distribution at steady state (Vd_{SS}) can be estimated from the equation (Shargel & Yu 1993):

$$Vd_{SS} = (\text{dose} \times \text{AUMC})/\text{AUC}^2 = \text{CL} \times \text{MRT} \quad (5)$$

where MRT is the mean residence time,

$$\text{MRT} = \text{AUMC}/\text{AUC} \quad (6)$$

and AUC and AUMC are area under the curve and area under the moment curve, respectively.

In interspecies scaling V_c, V_β and Vd_{SS} are predicted indiscriminately. Among all these volumes, V_c is the most important. Because the dose administered is always known, on the basis of a knowledge of V_c one can calculate the plasma concentration of a drug at time zero after intravenous administration. This initial plasma concentration can be important in establishing the safety or toxicity for first-time dosing in man. However, Vd_{SS} and V_β are of no real significance for first-time dosing in man; they can be estimated from the data from man. It is also possible that both Vd_{SS} and V_β might not be predicted as accurately as V_c.

MRT can be defined as the average time drug molecules spend in the body. MRT represents the time for 63·2% of a drug to be eliminated (Shargel & Yu 1993). In the one-compartment model MRT and half-life can be related by (Shargel & Yu 1993):

$$\text{MRT} = 1/k = 1{\cdot}44 \times t_{1/2} \quad (7)$$

In the two-compartment model MRT and half-life can be related by the equation (Shargel & Yu):

$$\text{MRT} = 1/\alpha + 1/\beta - 1/k_{21} \quad (8)$$

where α and β are the rate constants and k_{21} is the inter-compartmental rate constant.

Systematic extrapolation of MRT from animal data to man has not been evaluated. In this study an attempt has been taken to predict MRT in man from values measured in animals. Like clearance and volume, elimination half-life (t½) is also an important pharmacokinetic parameter. Generally there is poor cross-species correlation of the relationship between t½ and body weight, hence predicted t½ values are subject to gross error (McNamara 1991). This poor correlation might be because t½ is a hybrid parameter, not directly related to physiological function of the body (McNamara 1991). In a one-compartment model elimination half-life can be related to volume and clearance by the equation:

$$t_{1/2} = 0{\cdot}693V/\text{CL} \quad (9)$$

Besides predicting half-life by use of the allometric approach, half-life can also be extrapolated from animals to man by use of equation 9. Mahmood & Balian (1996a) compared the predictive performance of elimination half-life by use of equation 9 and by simple allometry (relationship between body weight and t½). The results indicated that t½ can be predicted reasonably well from equation 9, indeed better than by simple allometry, if reasonably accurate estimates of CL and V_c are obtained. Although equation 9 is only strictly true for a one-compartment model, the authors showed that for predictive purposes the equation can also be used for a two-compartment model.

The objectives of this study (using at least three animal species) were: to evaluate the necessity and accuracy of the prediction of V_c, V_β and Vd_{SS} in man from animal data; to predict MRT in man from animal data; to predict t½ from predicted MRT and compare with t½ predicted using simple allometry and; to compare t½ predicted by use of equation 9 with that predicted by simple allometry.

Methods

Data for V_c, V_β, Vd_{SS}, MRT and t½ were obtained from the literature. Table 1 summarizes drugs and species used in the analysis of volumes, mean residence time and half-life. V_c, V_β, Vd_{SS} and MRT

Table 1. Names of compounds and species used in the analysis of volumes, mean residence time and elimination half-life.

Drug	Species	Reference
Tolcapone	Rat, rabbit, dog	Lave et al (1996b)
Lamifiban	Rat, dog, cynomolgus monkey	Lave et al (1996a)
Interferon	Mouse, rat, rabbit, dog	Lave et al (1995)
AZT	Mouse, rat, dog, rhesus monkey	Patel et al (1990)
Erythromycin	Mouse, rat, rabbit, dog	Duthu (1985)
Oleandomycin	Mouse, rat, rabbit, dog	Duthu (1985)
Amascrine	Mouse, rat, rabbit, dog	Paxton et al (1990)
CI-921	Mouse, rat, rabbit, dog	Paxton et al (1990)
Sematilide	Rat, rabbit, dog	Hinderling et al (1993)
Sch-34343	Mouse, rat, rabbit, dog, cynomolgus monkey	Chung et al (1985)
Ciprofloxacin	Rat, rabbit, dog	Siefert et al (1986), Abadia et al (1994), Aramayona et al (1996), Drusano et al (1986), Wise (1984)
Cyclosporin	Rat, rabbit, dog	Awani & Sawchuk (1985), Gridelli et al (1986), Sangali et al (1988)
Cefotetan	Mouse, rat, rabbit, dog, rhesus monkey	Swada et al (1984)
Cefmetazole	Mouse, rat, rabbit, dog, rhesus monkey	Swada et al (1984)
Cefoperazone	Mouse, rat, rabbit, dog, rhesus monkey	Swada et al (1984)
Moxalactam	Mouse, rat, rabbit, dog, rhesus monkey	Swada et al (1984)
Cefpiramide	Mouse, rat, rabbit, dog, rhesus monkey	Swada et al (1984)
Cefazoline	Mouse, rat, rabbit, dog, rhesus monkey	Swada et al (1984)
Amphotericin B	Mouse, rat, dog, rhesus monkey	Hutchaleelaha et al (1997)
Remoxipride	Mouse, rat, dog	Widman et al (1993), Movin-Osswald & Hammarlund-udenaes (1991)
Caffeine	Mouse, rat, rabbit, rhesus monkey	Bonati et al (1984–85)
Acivicin	Mouse, rat, dog, rhesus monkey, cynomolgus monkey	McGovern et al (1988)
Theophylline	Mouse, rat, rabbit, dog	Bachmann (1989), Gascon et al (1994)
Antipyrine	Mouse, rat, rabbit	Bachmann (1989)
Warfarin	Rat, rabbit, dog	Bachmann (1989)
Valproic acid	Mouse, rat, dog	Loscher (1978)
Topiramate	Rat, rabbit, dog	Streeter (personal communication)
Ethosuximide	Rat, rabbit, dog	El Sayed et al (1978)

were estimated from equations 3–6, respectively, and plotted on log–log scale (parameter of interest against body weight). Data from man were not included in the scaling. The allometric equation thus generated was used to predict the pharmacokinetic parameters for man.

For the sake of simplicity equations 7 and 9 were used to predict half-life of drugs in man, irrespective of the number of compartments. To use equation 9, V_c and clearance were extrapolated from animals to man and then these predicted values were used to predict half-life for man.

Wherever necessary, the bias between the methods was estimated by calculating the mean prediction error (MPE). The accuracy of the method was measured by calculating mean absolute error (MAE).

$$\text{MPE} = \text{Sum (predicted} - \text{observed)/n}$$

$$\text{MAE} = \text{Sum |predicted} - \text{observed|/n}$$

Both MPE and MAE were expressed as the percent of the observed mean from:

$$((\text{MPE or MAE}) \times 100)/\text{observed mean}$$

Results

Tables 2 and 3 summarize the correlation coefficients and the exponents of the allometric equations and the predicted and observed values of V_c, V_β and Vd_{SS}. For all three volumes, an excellent relationship was observed between the body weight and the volume. For the majority of drugs the exponents of the allometric equations tend towards unity, indicating that volume was directly proportional to body weight. The volume of the central compartment was predicted for man with reasonable accuracy for all nine drugs. Vd_{SS} (MAE = 85%) and V_β (MAE = 72%) were predicted with less accuracy and higher percentage error than V_c (MAE = 33%).

Table 4 summarizes the observed and predicted values of MRT (n = 18). Except for cyclosporin and ciprofloxacin, excellent correlation was observed between body weight and MRT. The exponents of the allometric equation ranged from −0·260 to 0·381. With the exception of oleandomycin and CI-921, MRT was predicted with reasonable accuracy in man by use of the animal data. Despite the poor correlation between body weight and MRT for cyclosporin and ciprofloxacin, the predicted MRT was reasonable (predicted error

Table 2. Allometric exponents and correlation coefficients for volumes.

Drug	V_c		Vd_{SS}		V_β	
	Exponent	R	Exponent	R	Exponent	R
Erythromycin	0·912	0·938	0·901	0·986	0·932	0·989
Oleandomycin	0·852	0·954	0·787	0·986	0·804	0·998
Tolcapone	0·936	0·993	0·937	0·992	0·900	0·970
Amphotericin B	0·965	0·940	0·839	0·960	0·948	0·950
Remoxipride	0·962	0·958	0·877	0·993	0·809	0·998
Cyclosporin	0·947	0·848	0·950	0·907	0·928	1·000
Ciprofloxacin	0·760	0·983	0·962	0·970	0·974	0·998
Sch-34343	0·883	0·998	1·022	0·998	0·995	0·996
Cefpiramide	0·883	0·915	0·816	0·942	0·826	0·944

Table 3. Observed volumes in man and values predicted from animal data.

Drug	V_c			Vd_{ss}			V_β		
	Observed	Predicted	Error (%)	Observed	Predicted	Error (%)	Observed	Predicted	Error (%)
Erythromycin	55	91	65	62	195	215	93	233	151
Oleandomycin	58*	39	39	54	90	67	58	81	40
Tolcapone	5	7	40	9	13	44	13	22	69
Amphotericin B	53	65	23	224	87	61	266	172	35
Remoxipride	45	35	22	49	108	120	50	93	86
Cyclosporin	25	26	4	91	160	76	147	276	88
Ciprofloxacin	31	39	26	122	222	82	157	294	87
Sch-34343	3	5	67	24	15	38	49	21	57
Cefpiramide	4	5	25	8	8	0	8	9	13
% Bias		12			40			43	
% MAE		33			85			72	

The value for the volume of distribution in the central compartment for oleandomycin could not be found in the literature; it was therefore estimated from the equation CL = VK (Duthu (1985)).

Table 4. Observed mean residence time in man and values predicted from animal data.

Drug	MRT		Error (%)	R	Exponent
	Observed	Predicted			
Tolcapone	1·20	1·70	42	0·875	0·283
Lamifiban	2·50	4·10	64	0·915	0·385
Interferon	2·40	2·40	0	0·776	0·231
AZT	0·90	1·14	27	0·827	0·107
Erythromycin	2·10	3·20	52	0·883	0·137
Oleandomycin	1·40	3·10	121	0·851	0·123
Amascrine	6·00	8·20	37	0·975	0·381
CI-921	2·00	3·80	90	0·682	0·228
Sematilide	3·10	3·60	16	0·946	0·186
Sch-34343	0·73	0·83	14	0·963	0·317
Ciprofloxacin	4·80	2·95	39	0·132	0·037
Cyclosporin	5·50	2·90	47	0·337	−0·260
Cefotetan	4·40	2·10	52	0·906	0·339
Cefmetazole	1·28	0·87	32	0·886	0·220
Cefoperazone	2·30	2·50	9	0·853	0·351
Moxalactam	2·40	1·70	29	0·999	0·289
Cefpiramide	6·70	4·50	33	0·917	0·373
Cefazoline	2·00	1·75	13	0·914	0·241

Table 5. Half-lives predicted in man from animal data using simple allometry or mean residence time.

Drug	Observed half-life	Half-life predicted from allometry	Error (%)	R	Exponent	Half-life predicted from MRT	Error (%)
Tolcapone	1·30	2·10	62	0·986	0·246	1·20	8
Lamifiban	2·10	4·20	100	0·989	0·386	2·90	38
Interferon	5·10	4·80	6	0·631	0·211	1·63	68
AZT	1·10	0·64	42	0·513	−0·066	0·80	27
Erythromycin	2·20	2·34	6	0·936	0·143	2·20	0
Oleandomycin	1·00	1·90	90	0·999	0·126	2·10	110
Amascrine	4·70	15·30	226	0·984	0·547	5·70	21
CI-921	2·60	6·50	150	0·834	0·342	2·60	0
Sematilide	2·70	2·80	4	0·994	0·120	2·50	7
Sch-34343	1·00	0·80	20	0·933	0·286	0·60	40
Ciprofloxacin	4·30	2·50	42	0·259	0·039	2·05	52
Cyclosporin	6·20	4·30	31	0·594	−0·236	2·00	68
Cefotetan	3·40	1·70	50	0·900	0·280	1·50	56
Cefmetazole	0·90	1·20	33	0·944	0·322	0·60	33
Cefoperazone	2·35	2·40	2	0·798	0·316	1·80	23
Moxalactam	1·30	1·80	38	0·964	0·242	1·70	31
Cefpiramide	5·00	3·80	24	0·928	0·385	3·10	38
Cefazoline	1·50	1·40	7	0·946	0·260	1·20	20
% Bias		24				−26	
% MAE		55				39	

Table 6. Observed half-life and values predicted using the equation CL = VK.

Drug	Observed half-life	Half-life predicted from volume	Error (%)	Half-life predicted from allometry	Error (%)
Cyclosporin	6·2	1·1	82	4·3	31
Ciprofloxacin	4·3	1·3	70	2·5	42
Caffeine	4·9	10·9	122	4·8	2
Acivicin	9·5	7·6	20	6·4	33
Erythromycin	2·2	2·7	23	2·3	5
Oleandomycin	1·0	1·0	0	2·0	100
Theophylline	9·0	8·0	11	10·0	11
Antipyrine	12·2	12·3	1	7·0	43
Warfarin	37·5	37·3	1	7·5	80
Sch-34343	1·0	0·8	20	0·8	20
Valproic acid	14·0	14·1	14	2·8	80
Topiramate	21·0	17·5	28	4·5	79
Ethosuximide	45·0	60·0	33	12·0	73
Remoxipride	4·8	2·5	48	3·2	33
Cefpiramide	3·9	2·1	46	3·8	3
% Bias		2		−58	
% MAE		23		61	

< 50%). Overall, the predicted error for 13 out of 18 drugs was less than 50%.

Table 5 summarizes the predicted half-lives of 18 drugs calculated using simple allometry and from MRT using equation 7. There was good correlation between half-life and body weight. Reasonably accurate prediction was observed with renally excreted drugs. However, for drugs which are mainly metabolized, for example tolcapone, lamifiban, oleandomycin, amascrine, and CI-921, the predicted half-life was in gross error. When half-life was predicted from MRT using equation 7, the quality of the prediction was improved (smaller percentage error) for extensively metabolized drugs but there was no improvement for renally excreted drugs. The bias between the predicted half-life from the allometric equation and from MRT was similar, but MAE was much smaller for the half-lives predicted from MRT (39%) than for those predicted from the allometric equation (55%). Half-life was also predicted from equation 9 (Table 6). The results indicated that the error in half-life predicted by use of equation 9 was much smaller than that predicted from allometric equation. There was negligible bias in the prediction of half-life from equation 9 and the accuracy of the prediction was much higher (MAE = 23%) than that obtained from the allometric equation (MAE = 61%).

Discussion

To enable design of safe first-time dosing regimens for man considerable attention has, in recent years, been devoted to prediction of pharmacokinetic parameters (CL, V, and t½) in man from animal data. Although much effort has been devoted to improving the predictive performance of clearance, half-life has attracted less attention. This might be because of the hybrid nature of half-life, a firm relationship between half-life and body weight could not be established.

Elimination half-life is occasionally difficult to extrapolate across species. Allometric relationships are not governed by physiological or biological laws (Lindstedt & Calder 1981), hence good correlation (r) between body weight and the pharmacokinetic parameter of interest does not necessarily mean that a real physiological relationship exists. It is apparent from Table 5 that although the correlation coefficients (r) for tolcapone, lamifiban, oleandomycin and amascrine were $> 0{\cdot}9$, the error in predicted half-life was $> 60\%$. Values for drugs such as interferon and cefperazone were accurately predicted even though the correlation coefficient for these two drugs was $< 0{\cdot}8$.

Despite difficulties in establishing a relationship between half-life and body weight, half-lives of many drugs have been successfully predicted by allometric scaling. Table 5 of this study indicates that the half-life was reasonably accurately predicted for renally excreted drugs (β-lactams, sematilide, ciprofloxacin and interferon). Values for drugs which are mainly excreted after metabolism (tolcapone, lamifiban, erythromycin, amascrine, CI-921) were predicted with less accuracy than those for renally excreted drugs. In a separate study, Mahmood & Balian (1996a) noted that the half-lives of valproic acid, ethosuximide, diazepam, progabide and AD-810, which are extensively metabolized, could not be predicted by simple allometry.

An alternative to allometry, prediction of half-life using equation 9, $CL = VK$, has been investigated by Bachmann (1989) and Mahmood & Balian (1996a). Table 6 compares the half-lives predicted by simple allometry and by use of equation 9. It is apparent that equation 9 predicts the half-life with less error than the allometric equation.

For the first time a systematic evaluation of the prediction of MRT in man from animal data has been attempted in this study. The results show that MRT can be predicted with reasonable accuracy in man. Although only 18 drugs have been used in this evaluation, it seems that MRT can be predicted with more precision than half-life. This should not be surprising because MRT is the ratio of AUMC to AUC, whereas half-life is a hybrid rate constant which might not be related to body weight as well as MRT. In this study, attempts were also made to predict half-life from predicted MRT. Table 5 compares the half-lives predicted by allometry and from MRT (equation 7). The results indicate that half-lives of drugs which are mainly excreted by metabolism can be predicted better from MRT than by simple allometry. On the other hand, both the allometric approach and MRT can be used for the prediction of half-life for renally excreted drugs.

Like clearance and half-life, V_c is also an important pharmacokinetic parameter. A survey of the literature indicates that attempts have been made to predict not only V_c, but also Vd_{SS} and V_β. From Table 3, it seems that neither Vd_{SS} nor V_β can be predicted as accurately as V_c. This might be because estimation of both Vd_{SS} and V_β includes clearance (equations 4 and 5). If clearance in man cannot be predicted with reasonable accuracy then the probability of accurate prediction of Vd_{SS} and V_β might be low. Furthermore, Vd_{SS} and V_β are of no real significance for first-time dosing in man and can be estimated from the data obtained from man.

Conclusions

The results of this study indicate that animal MRT data can be used to predict MRT in man with sufficient accuracy. The predicted MRT can be used to predict half-life in man. From a survey of the literature and from this study it seems that half-life can be predicted reasonably well for renally excreted drugs but this might not be true for drugs which are eliminated after metabolism. In addition to the use of the allometric equation and MRT, half-life can also be predicted by use of equation 9. It is suggested that to extrapolate half-life from animals to man, all three approaches mentioned in this report should be used. This approach will provide a broader view of the half-life of a drug in man. For volume, emphasis should be on V_c rather than Vd_{SS} and V_β, not only because V_c can be predicted more accurately than Vd_{SS} and V_β, but can also be used to predict maximum plasma concentration after intravenous administration.

It should be noted that allometric extrapolation is affected by experimental design, species, analytical errors, variation in pharmacokinetic parameters from one laboratory to another, and the weight-range of the species under study. Therefore, all these methods should be used with caution and proper understanding of allometric scaling. Furthermore, the use of fixed exponents for clearance (0·75), volume (1·0) and half-life (0·25) should be avoided.

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