CAN ABSOLUTE ORAL BIOAVAILABILITY IN HUMANS BE PREDICTED FROM ANIMALS? A COMPARISON OF ALLOMETRY AND DIFFERENT INDIRECT METHODS

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SUMMARY

The objective of this study was to predict absolute bioavailability in humans from animal data using interspecies scaling as well as indirect approaches. Five different methods were used to predict absolute bioavailability in humans: (i) absolute bioavailability vs body weight (allometric approach); (ii) $F = CL_{(IV)}/CL_{(oral)}$; (iii) $F = 1-[CL_{(IV)}/Q]$; (iv) $F= 1-[CL_{(oral)}/Q]$; and (v) $F = Q/[Q+CL_{(oral)}]$. Methods II-V are indirect approaches, where predicted i.v. or oral clearance and hepatic blood flow (Q) (1500 ml/min) were used to predict absolute bioavailability in humans. Fifteen drugs were tested and the results of this study indicate that all five approaches predict absolute bioavailability with different degrees of accuracy, and are therefore unreliable for the accurate prediction of absolute bioavailability in humans from animal data. In conclusion, although the above-mentioned approaches do not accurately predict absolute bioavailability, a rough estimate of absolute bioavailability is possible using these approaches.

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KEY WORDS

allometric scaling, absolute bioavailability, clearance, liver blood flow

INTRODUCTION

Interspecies scaling has been successfully used to predict pharmacokinetic parameters (clearance, volume of distribution and half-life) from animals to humans and such extrapolations are invaluable during drug development. Utilizing the concept of allometry, the absolute oral bioavailability (F) in humans may be predicted from animal data. Due to differences in the anatomical and physiological features of the gastrointestinal tract, dietary habits, blood flow through the gut and the liver, and the enzymatic activity of metabolizing enzymes, the oral absorption of drugs varies among species. Therefore, the rate (C_{max}) and the extent of a drug's absorption (absolute bioavailability) varies from species to species. Due to these complexities, prediction of absolute bioavailability in humans from animal data may not be as straightforward as it appears and, therefore, animal models can only provide a rough estimate of absolute bioavailability in humans. Even such rough estimates can be of significant importance to identify problems of absorption and intestinal and hepatic metabolism in man. Since in an allometric approach, one tries to relate body weight to the parameter of interest, conceptually it is difficult to justify that an allometric relationship may exist between body weight and absolute bioavailability. However, a systematic study in this direction is lacking. The objective of this study was to evaluate the predictive performance of allometry to predict absolute bioavailability from animals to humans. Furthermore, four indirect methods were also evaluated to predict absolute bioavailability in humans from animal data.

METHODS

A literature search was conducted to obtain absolute bioavailability values for drugs that have been studied in at least three animal species (mouse, rat, rabbit, guinea-pig, monkey or dog). Fifteen drugs were selected randomly and the scaling of absolute bioavailability was performed as follows:

Method I

Absolute bioavailability of each drug was plotted against body weight on a log-log scale and the following allometric equation was used to predict bioavailability in humans.

$$F = a\,(W)^b \quad (1)$$

where W is body weight and a and b are the coefficient and exponent of the allometric equation, respectively.

Methods II-V

In these four indirect methods of absolute bioavailability prediction, the systemic and/or oral clearance of drugs is required. These predicted plasma clearances were then used to predict absolute bioavailability using equations 6-9. The following three approaches were used to predict clearance in humans:

(i) Simple allometry

Clearance of each drug was plotted against body weight on a log-log scale and the following allometric equation was used to predict clearance in humans:

$$\text{Clearance} = a\,(W)^b \quad (2)$$

where W is body weight and a and b are the coefficient and exponent of the allometric equation, respectively.

(ii) Maximum life-span potential (MLP)

The observed clearance values in the different animal species were multiplied by their respective maximum life-span potential (MLP) and were plotted as a function of body weight on a log-log scale. From this plot, clearance x MLP was estimated in humans and the result was then divided by the MLP of humans (8.18×10^5 h) to predict clearance in man.

$$\text{Predicted CL in humans} = \frac{\text{MLP} \times \text{Clearance}}{8.18 \times 10^5} \quad (3)$$

MLP in years was calculated from the following equation as described by Sacher /1/:

$$MLP\ (years) = 185.4\ (BW)^{0.636}\ (W)^{-0.225} \quad (4)$$

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

(iii) Product of brain weight and clearance

In this approach, clearance of animal species was multiplied by the brain weight of the species and the product was plotted as a function of body weight on a log-log scale. From this plot, clearance x brain weight was estimated in humans and the result was then divided by the human brain weight (1.53 kg).

$$\text{Predicted CL in humans} = \frac{\text{brain wt x Clearance}}{1.53} \quad (5)$$

Both systemic and oral clearance were predicted in humans using the approach as described by Mahmood and Balian /2/.

The following equations were used to predict bioavailability of studied drugs indirectly from the predicted clearance:

Method II

$$F = \frac{CL(IV)}{CL(oral)} \quad (6)$$

Method III

$$F = \frac{1 - CL(IV)}{Q} \quad (7)$$

where Q is hepatic blood flow (1500 ml/min).

Method IV

$$F = \frac{1 - CL(oral)}{Q} \quad (8)$$

Method V

$$F = \frac{Q}{Q + CL(oral)} \quad (9)$$

A number of assumptions were made while using equations 7-9. Equations 7-9 only represent hepatic bioavailability. Absolute

bioavailability may depend on the fraction of the drug absorbed by the gastrointestinal tract, metabolism by the liver, or by both the liver and the gut. Since all this information may not be available during the early phase of drug development, equations 7-9 will merely provide a rough estimate of absolute bioavailability. Furthermore, for equations 7-9, total clearance rather than hepatic clearance was used.

Statistical analysis

Mean absolute error (MAE) was used to compare the predictive performance of different methods.

$$MAE = \frac{\sum i = 1 \ | \text{predicted - observed} |}{n}$$

MAE was expressed as the percent of the observed mean as follows:

$$\frac{(MAE) * 100}{\text{observed mean}}$$

RESULTS

Method I

Table 1 summarizes the exponents of the allometry and the correlation coefficients between body weight and absolute bioavailability. A correlation coefficient greater than 0.8 was observed for 8 out of 15 drugs. The exponents of allometric equation widely varied and were found to be both negative and positive. Table 1 also summarizes the predicted and observed absolute bioavailability of 15 drugs. Irrespective of a weak or strong relationship between body weight and absolute bioavailability, unreliable prediction of absolute bioavailability was obtained using the allometric approach. The error between predicted and observed bioavailability ranged from 0% to 265%.

Methods II-V

In order to predict absolute bioavailability indirectly, the predicted systemic and oral clearances were used. Table 2 provides the summary of the exponents of the allometry and the correlation coefficients between body weight and clearance following i.v. and oral administration. Table 2 also compares the predicted and observed clearance.

TABLE 1

Predicted and observed absolute bioavailability using allometric approach

Drug	Exponent	Corr Coeff (R)	Obs F (%)	Pred F (%)	Reference
Actisomide	0.407	0.993	30-43	135	5
Amlodipine	-0.021	0.908	63	86	6
Candoxatrilat	-0.221	0.907	32	15	7
CI-1007	-0.074	0.110	4	12	8
Dofetalide	0.036	0.286	83	66	9
Faradifiban	-0.212	0.557	24	5	10
Meloxicam	-0.002	0.140	95	89	11-12
Metoprolol	0.144	0.613	38	53	13-16
Morphine	-0.140	0.886	24	9	17
Nicardipine	-0.229	0.743	7	9	18
Recainam	0.170	0.952	67	132	19
Remikiren	-0.368	0.652	0.3	0.3	20-21
Sildenafil	0.184	0.994	35	70	22
Tacrolimus	-0.065	0.998	25	8	24-26
Troglitazone	0.168	0.860	43-53	53	27-28

TABLE 2

Predicted and observed clearance of 15 drugs following intravenous and oral administration

Drug	Intravenous				Oral			
	Exponent	R	Obs CL	Pred CL	Exponent	R	Obs CL	Pred CL
Actisomide	1.066	0.993	475	531	0.648	0.961	920-1465	703
Amlodipine	0.821	0.924	490	324	0.843	0.931	778	375
Candoxatrilat	0.700	0.998	133	198	0.926	0.987	416	356
CI-1007	0.905	0.999	1120	1028	1.134	0.997	26229	27113
Dofetalide	0.519	0.969	393	281	0.481	0.999	474	390
Faradifiban	0.776	0.999	98	88	0.858	0.975	410	605
Meloxicam	0.860	0.933	11	7	0.882	0.945	12	8
Metoprolol	0.428	0.962	1050	826	0.286	0.976	2763	1547
Morphine	1.000	0.997	1300	1015	0.828	1.000	4483	6611
Nicardipine	0.546	0.962	630	790	0.818	0.998	9170	8665
Recainam	0.601	0.996	500	472	0.431	1.000	725	364
Remikiren	0.571	0.947	891	701	0.920	0.964	297000	214667
Sildenafil	0.680	1.000	420	523	0.496	0.997	1185	775
Tacrolimus	1.300	0.957	2100	2300	1.573	0.984	2800-25205	43875
Troglitazone	0.824	0.993	353-435	193	0.633	0.984	821	793

Based on the exponents, one of the three methods (as described earlier) was used for the prediction of clearance. Simple allometry, MLP and brain weight approach were used when the exponents of simple allometry were ≤0.7, 0.71-0.99, and ≥1.0, respectively /2/. Both systemic and oral clearance were predicted with reasonable accuracy (prediction error less than 30%) for most of the drugs used in the study. The four indirect approaches predicted bioavailability with different degrees of accuracy (Table 3). The overall results of the study indicate that none of the methods used in this study to predict bioavailability is reliable. However, a rough estimate of bioavailability can be obtained by using all five approaches and taking the midpoint of the lowest and the highest predicted bioavailability. In this study the midpoint used was the average of the lowest and the highest values. Some unreasonable predictions (>100%), as seen with actisomide and recainam, were omitted from this analysis. Based on %MAE (Table 3), it can be seen that the prediction of absolute bioavailability using the allometric approach is the worst, whereas the best estimate was obtained using the midpoint approach.

DISCUSSION

Pharmacokinetics plays an important role during drug development. Characterization of absorption, distribution, metabolism and excretion (ADME) in animals is of fundamental importance. The pharmacokinetic parameters from animals are extrapolated to humans for the selection of a suitable dose for the first dosing trials in humans. This report emphasizes the role and limitations of animal models to extrapolate absolute bioavailability in humans. It should be noted that one of the major drawbacks of extrapolating absolute bioavailability from animals to humans is that the animals may receive a different dosage form than humans. Generally animals are given an oral dose in solution form, whereas humans receive an oral dose as a tablet or capsule. This study assumes that the relative bioavailability between solid and liquid dosage forms is similar. Furthermore, the objective of extrapolating absolute bioavailability from animals to humans may not be to predict absolute bioavailability precisely (mainly due to the inherent difficulties described earlier), but rather to obtain a rough estimate of absolute bioavailability in humans.

TABLE 3

Predicted and observed absolute bioavailability of 15 drugs using different methods

Drug	Obs F (%)	Predicted F (%)						
		Method I	Method II	Method III	Method IV	Method V	Range	Mid point
Actisomide	30-43	135	76	65	53	68	53-76	64
Amlodipine	63	86	86	78	75	80	75-86	80
Candoxatrilat	32	15	56	87	75	81	15-87	51
CI-1007	4	12	4	31	NA	5	5-31	18
Doftalide	83	66	72	81	74	79	66-81	74
Faradifiban	24	5	15	94	60	71	5-94	50
Meloxicam	95	89	89	99	99	99	89-99	94
Metoprolol	38	53	53	45	NA	50	45-53	49
Morphine	24	9	16	32	NA	19	9-32	20
Nicardipine	7	9	9	47	NA	15	9-15	12
Recainam	67	132	130	69	76	81	69-81	75
Remikiren	0.3	0.3	0.3	47*	NA	0.7	0.3-0.7*	0.50
Sildenafil	35	70	67	65	48	65	48-70	59
Tacrolimus	25	8	5	NA	NA	3	3-8	5
Troglitazone	43-53	53	23	88	47	15	23-88	55
% MAE		**59**	**46**	**58**	**NC**	**49**		**33**

NC = not calculated because there were only 9 drugs available for this method. NA = not available - oral clearance was greater than hepatic blood flow (1500 ml/min). *Method III not included in the analysis.
Method I = body weight vs absolute bioavailability; Method II: F = CL(IV)/CL(oral); Method III: F = 1-[CL(IV)/Q]; Method IV: F= 1-[CL(oral)/Q]; Method V: F = Q/[Q+CL(oral)].

Though a lot of attention has been given to predicting pharmacokinetic parameters such as clearance, volume of distribution and half-life in humans from animals, not much attention has been paid to predicting absolute bioavailability in humans. This may be due to the fact that the anatomy and physiology of animals vary widely and hence the absorption of an oral dose varies across species. Furthermore, the concept that absolute bioavailability can be related to body weight is not convincing. The results of this study clearly demonstrate the above-mentioned concerns. The relationship between body weight and absolute bioavailability (as determined by R) was found to be highly variable. For some drugs a good correlation (>0.8) was obtained, but a good correlation itself is no guarantee of a good prediction of absolute bioavailability. For example, correlation of 0.95 and greater was obtained for actisomide, recainam and tacrolimus, and yet the predicted absolute bioavailability was in gross error. The exponents of the allometry also fluctuated between positive and negative values with no particular trend for a given drug. In short, reliable predictions of absolute bioavailability were not obtained using an allometric approach.

Equations 6-9 have been suggested as indirect methods to estimate absolute bioavailability /3/. Obach *et al.* /4/ used equation 7 to obtain a rough estimate of absolute bioavailability and reported that this approach predicted absolute bioavailability with a fair degree of accuracy. Besides the approach of Obach *et al.*, in this report equations 8 and 9 were also evaluated for an indirect estimate of absolute bioavailability in humans. Equations 6-9 assume that the drug is completely absorbed and is not metabolized by the gut. Overall, it can be seen that an indirect approach, like the allometric approach (body weight vs absolute bioavailability), also exhibits uncertainty about the prediction of absolute bioavailability. Equation 6 requires an accurate prediction (probably less than 10% error between observed and predicted values) of clearance following both i.v. and oral administration for a precise prediction of absolute bioavailability. Equations 7-8 have their limitations. When the clearance is more than hepatic blood flow, this approach cannot be used. It should be noted that the reported clearance of the studied drugs is plasma clearance rather than blood clearance. Q is the hepatic blood flow (1500 ml/min) and has been used for the calculation of absolute bioavailability using equations 7-9. Although not reported here, the use of hepatic plasma

flow (approximately 750 ml/min) in place of hepatic blood flow did not help in improving the prediction of absolute bioavailability.

At this time, due to the lack of appropriate method(s), the only possibility is to obtain a rough estimate of absolute bioavailability from animal data. Since all five methods were found unreliable, a rough estimate of absolute bioavailability can be achieved by using all five methods and taking the midpoint of the lowest and the highest predicted absolute bioavailability. In practice, a precise prediction of absolute bioavailability may not be necessary, but rather a rough estimate may suffice for making decisions during drug development.

Overall, this study indicates that the allometric as well as indirect approaches may not predict the absolute bioavailability in humans with any degree of accuracy. However, this conclusion has been drawn based on very limited data (n = 15). Furthermore, the purpose of this preliminary report is to incite investigators of allometric scaling to further work in this direction.

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