INTERSPECIES SCALING: IS *A PRIORI* KNOWLEDGE OF CYTOCHROME P450 ISOZYMES INVOLVED IN DRUG METABOLISM HELPFUL IN PREDICTION OF CLEARANCE IN HUMANS FROM ANIMAL DATA?*

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SUMMARY

The objective of this study was to evaluate whether *a priori* knowledge of cytochrome P450 isozymes involved in drug metabolism coupled with Mahmood' and Balian's 'rule of exponents' can be helpful for the prediction of clearance in humans using animal data. The clearance of 27 randomly selected drugs metabolized by different isozymes were scaled up from the animal data (at least three animal species) obtained from the literature. Three methods were utilized to generate allometric equations to scale up the clearance values: (i) clearance vs body weight (simple allometry); (ii) product of the clearance and maximum life-span potential (MLP) vs body weight; and (iii) the product of clearance and brain weight vs body weight. The choice of one of the methods was based on the 'rule of exponents' as described by Mahmood and Balian. The results of this study indicate that the knowledge of a particular isozyme does not provide a guide for the failure or success of allometry for the prediction of clearance. There is no trend which indicates that the chances of accurate prediction of clearance for a given drug are comparatively higher or lower when they are metabolized by a particular isozyme.

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KEY WORDS

allometric scaling, drug metabolism, cytochromes P450, clearance, bioavailability

INTRODUCTION

Allometry is based on the assumption that the relationships between anatomy and physiological functions are similar among mammalian species /1/. Over the years, allometry has become a useful tool for correlating pharmacokinetic parameters with body weight from different animal species. By establishing such a correlation, one can predict pharmacokinetic parameters in humans which can be useful during drug development.

Clearance (CL) is a very important pharmacokinetic parameter and a lot of attention has been given to the prediction of clearance in humans from animal data. A review of the literature indicates that simple allometry is not adequate to predict clearance for every drug /2,3/. To improve the predictive performance of allometry for the prediction of clearance, several different approaches have been proposed, such as: (i) using species weight and maximum life-span potential (MLP) /4/; (ii) using a two-term power equation based on brain weight and body weight /5/; (iii) using the product of CL x brain weight /2,3/; and (iv) using normalized *in vivo* clearance by *in vitro* clearance versus body weight /6-8/. In a previous study, Mahmood and Balian /2,3/ evaluated the different circumstances under which one of three different methods (simple allometry, CL x MLP, or CL x brain weight) is most suitable for the improved prediction of clearance in humans. They proposed the selection of one of the methods based on the exponents of simple allometry: (i) if the exponent of the simple allometry lies between 0.55 to 0.70, simple allometry will predict clearance more accurately than CL x MLP or CL x brain weight; (ii) if the exponent of simple allometry lies between 0.71 and 1.0, the CL x MLP approach will predict clearance better than simple allometry or CL x brain weight; and (iii) if the exponent of the simple allometry is >1.0, the product of CL x brain weight is a suitable approach to predict clearance in humans compared to the other two methods. The proposed 'rule of exponents' by Mahmood and Balian has helped a great deal in improving the predictive performance of allometry for

clearance. Despite the success of the 'rule of exponents' in prediction of clearance in humans from animals, there are still many drugs whose clearance cannot be predicted with reasonable accuracy (arbitrary selected, 30% or less difference between observed and predicted clearance). Furthermore, the success or failure of allometry for the prediction of clearance is arbitrary and has not been related to a particular class of drugs.

Human liver microsomes contain different cytochrome P450 isozymes which are responsible for the biotransformation of xenobiotics and endogenous substances. With the understanding of the role of cytochrome P450 (CYP) in the biotransformation of drugs it is possible to characterize the metabolic pattern of a drug. Analysis of the literature indicates that there are several isozymes (CYP3A4, CYP2D6, CYP2C9, CYP1A2, CYP2C19). There are, however, three major isozymes (CYP3A4, CYP2D6, CYP2C9) which are responsible for the metabolism of almost 90% of drugs /9/. Due to broad and overlapping specifications, sometimes two or more isozymes are involved in the metabolism of a particular drug /9/. The present report is an attempt to identify whether *a priori* knowledge of the cytochrome P450 isozymes involved in the metabolism of a particular drug can help to identify the success or failure of the allometric method for the prediction of clearance, i.e., to determine whether there is a systematic trend which can indicate that the clearance of a drug metabolized by a particular isozyme can or cannot be predicted with reasonable accuracy in humans. This may be also useful to identify the occasional failure of the 'rule of exponents'.

METHODS

A literature search was conducted to obtain clearance data on a wide variety of drugs that have been studied in at least three species (mice, rat, rabbit, guinea-pig, monkey, or dog). These drugs were selected randomly. In this analysis, there are 12 drugs which are mainly metabolized by CYP3A4, six drugs metabolized by CYP2D6 and nine drugs metabolized by more than one isozyme (e.g. CYP2C9, CYP2C19, CYP3A4 and CYP2D6). Based on the availability of data, wherever possible both systemic and oral clearance were predicted.

The allometric equation for clearance was generated using at least three animal species (human data were not included in the scaling) by

the following three methods, and the predicted values were compared with the reported values in humans.

Method I

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

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

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

Method II

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

$$CL = a\,(W)^b / 8.18 \times 10^5 \quad (2)$$

The maximum life-span potential (MLP) in years was calculated from the following equation as described by Sacher /10/:

$$MLP\ (years) = 185.4\,(BW)^{0.636}\,(W)^{-0.225} \quad (3)$$

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

Method III

Clearance of each animal 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. The allometric equation was then used to predict the clearance in man using the brain weight (1.53 kg) of humans.

$$CL = a\,(W)^b / 1.53 \quad (4)$$

The choice of one of the above mentioned methods was based on Mahmood's and Balian's rule of exponents as described previously.

RESULTS

A good correlation (r = >0.9) between body weight and clearance was observed for drugs which are metabolized by CYP3A4 (with the exception of indinavir, r = 0.592). The exponents of simple allometry ranged from 0.349 to 1.300 following i.v. administration (Table 1). The six drugs for which clearance values were available following oral administration also exhibited a strong correlation between body weight and clearance. The exponents of allometry ranged from 0.715 to 1.573. Using the rule of exponents, both the systemic and oral clearances were predicted with a fair degree of accuracy.

With the exception of two drugs (remoxipride [r = 0.523] and venlafaxine [r = 0.764] following oral administration), a good correlation between body weight and clearance was observed for drugs which are metabolized by CYP2D6 (Table 2). The exponents of simple allometry following i.v. and oral administration ranged from 0.428 to 0.905 and from 0.07 to 1.134, respectively. With the exception of propafenone, the predicted clearance of all drugs metabolized by CYP2D6 was comparable with the observed clearance. It is interesting to note that the exponent of remoxipride following oral administration was 0.07, and yet a reasonable prediction of remoxipride clearance was observed in humans. This may be a chance occurrence rather than the fact that clearance can be predicted reasonably well with such a low exponent.

It should be noted that the observed clearance values in animals did not differentiate between extensive or poor metabolizers. Furthermore, the reported clearance values in humans, with the exception of propafenone, did not identify poor or extensive metabolizers.

Drugs which are metabolized by more than one isozyme (e.g. CYP2C9, CYP2D6, CYP3A4) exhibited a strong correlation between body weight and clearance (Table 3). The exponents of allometry ranged from 0.496 to 1.126 following either i.v. or oral administration. The predicted systemic or oral clearances for drugs analyzed in this study were fairly accurate (with the exception of troglitazone and diazepam following i.v. and citalopram following oral administration). The results indicated that the clearance of drugs which are metabolized by more than one isozyme can also be predicted in humans with a fair degree of accuracy.

TABLE 1

Predicted and observed clearance (ml/min) of drugs metabolized by CYP3A4 following intravenous and oral administration

Drug	Intravenous				Oral				Ref.
	Exponent	R	Obs CL	Pred CL	Exponent	R	Obs CL	Pred CL	
Amlodipine	0.821	0.924	490	324	0.843	0.931	778	375	12
Cyclophosphamide	0.863	0.989	200	264	NA	NA	NA	NA	4
Cyclosporine	1.146	0.965	273	111	NA	NA	NA	NA	15
Diltiazem	NA	NA	NA	NA	0.813	0.990	1700-2500	3461	14
Erythromycin	0.807	0.990	492	418	NA	NA	NA	NA	15
Ethosuximide	0.520	0.987	10.7	10.0	NA	NA	NA	NA	16
Indinavir	0.349	0.592	1325	872	NA	NA	NA	NA	17-18
Nicardipine	0.546	0.960	630	790	0.818	0.998	9170	8665	19
Quinidine	0.805	0.960	330	285	NA	NA	NA	NA	20-23
Tacrolimus	1.300	0.957	2100	2300	1.573	0.984	2800-25205	43875	24-27
Topiramate	NA	NA	NA	NA	0.715	0.999	22-36	50	28
Zonisamide	NA	NA	NA	NA	0.735	0.987	17	20	29

NA = not applicable.

TABLE 2

Predicted and observed clearance (ml/min) of drugs metabolized by CYP2D6 following intravenous and oral administration

Drug	Intravenous				Oral				Ref.
	Exponent	R	Obs CL	Pred CL	Exponent	R	Obs CL	Pred CL	
CI-1007	0.905	0.999	1120	1028	1.134	0.997	26229	27113	30
Metoprolol	0.428	0.962	1050	826	0.286	0.976	2763	1547	31-34
Minaprine	NA	NA	NA	NA	0.668	1.000	231	248	35
Propafenone	0.827	0.827	1104*	550	NA	NA	NA	NA	36-37
Remoxipride	0.500	0.938	119	161	0.07	0.523	125	87	38
Venlafaxine	NA	NA	NA	NA	0.729	0.764	2217	1915	39-40

NA = not applicable.

* The clearance of propafenone in a recent paper [37] has been reported as 616 ml/min in extensive metabolizers and 201 ml/min in poor metabolizers.

TABLE 3

Predicted and observed clearance (ml/min) of drugs metabolized by several isozymes following intravenous and oral administration

Drug	Intravenous				Oral				Ref.
	Exponent	R	Obs CL	Pred CL	Exponent	R	Obs CL	Pred CL	
Caffeine	0.748	0.981	98	71	NA	NA	NA	NA	41
Citalopram	0.724	0.994	350	455	0.789	0.993	440	1252	42
Diazepam	0.737	0.939	26	466	NA	NA	NA	NA	43
Meloxicam	0.860	0.933	11	7	0.882	0.945	12	8	44-45
Propranolol	0.662	0.918	1050	840	NA	NA	NA	NA	46
Sildenafil	0.680	1.000	420	523	0.496	0.997	1185	775	47
Theophylline	0.657	0.954	42	46	NA	NA	NA	NA	48
Troglitazone	0.824	0.993	353-135	193	0.633	0.934	821	793	49-50
Warfarin	1.126	0.928	4	8	NA	NA	NA	NA	51

NA = not applicable.

DISCUSSION

Over the years allometric scaling is becoming a useful tool for the selection of a first time dose to be administered to humans /11/. The selection of such a dose may be based on the prediction of pharmacokinetic parameters such as clearance, volume of distribution and half-life. The knowledge of clearance is especially important during drug discovery or screening processes, 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 dosage in humans (as the 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. Despite many suggested approaches, there are many drugs whose clearance cannot be predicted with reasonable accuracy.

Over the span of the last 15 years, considerable progress has been made in the characterization of human cytochrome P450s. This knowledge is vital in determining the P450 enzymes responsible for the metabolism of a given drug. The assessment of the human P450 involved in drug metabolism can have significant impact in drug development. In this report, an attempt has been made to link the knowledge of a particular isozyme responsible for the metabolism of a drug and the predictive performance of allometry for clearance. This approach may serve as a flag and caution the investigator for the reliability of the predicted clearance.

Overall, the results of this study indicate that *a priori* knowledge of a given isozyme(s) is no guide in identifying the failure or success of allometry for the prediction of clearance. Furthermore, this knowledge was also no guide to the choice of scaling method (simple allometry, MLP or brain weight approach) as proposed by Mahmood and Balian /3/. The exponents of the drugs varied widely irrespective of the isozyme(s) responsible for their metabolism. There was no systematic trend with a given isozyme which can indicate that caution should be exercised for the prediction of clearance in humans from animals if that particular isozyme is responsible for the metabolism of the given drug. However, this conclusion has been drawn based on limited data (27 drugs), and therefore further investigation is warranted in this direction, especially for those drugs which are metabolized by

CYP2D6. Probably the predicted clearance for drugs which are exclusively metabolized by CYP2D6 will be closer to the clearance of extensive rather than poor metabolizers. The study also indicates that irrespective of the isozyme involved in drug metabolism, the rule of exponents can be applied to achieve a reasonable prediction of the clearance of drugs.

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