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A NOVEL MODEL FOR PREDICTION OF HUMAN DRUG CLEARANCE BY ALLOMETRIC SCALING

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ABSTRACT:

Sixty-one sets of clearance (CL) values in animal species were allometrically scaled for predicting human clearance. Unbound fractions (f_u) of drug in plasma in rats and humans were obtained from the literature. A model was developed to predict human CL: CL = 33.35 ml/min × $(a/Rf_u)^{0.770}$, where Rf_u is the f_u ratio between rats and humans and *a* is the coefficient obtained from allometric scaling. The new model was compared with simple allometric scaling and the "rule of exponents" (ROE). Results indicated that the new model provided better predictability for human values of CL than did ROE. It is especially significant that for the first time the proposed model improves the prediction of CL for drugs illustrating large vertical allometry.

Allometric scaling is widely used in predicting human clearance (CL) based on animal data. Since prediction errors are commonly observed in the practical application of this approach, various modifications to allometric scaling have been proposed. These modifications include in vitro metabolic data (Lave et al., 1997), correction by either maximum life-span potential (MLP) or brain weight (BrW) (Mahmood and Balian, 1996b), the "rule of exponents" (ROE) (Mahmood and Balian, 1996a), and scaling unbound CL (Feng et al., 2000). Correction by in vitro metabolic data was successful in predicting human CL of 10 extensively metabolized drugs (Lave et al., 1997). Based on a data analysis of 16 drugs, however, Mahmood (2002) concluded that the use of in vitro data obtained from liver microsomes to predict hepatic CL in humans did not provide reliable predictions. In addition, in vitro metabolic corrections cannot be applied to compounds eliminated by excretion. Scaling unbound CL across animal species improved the prediction for certain compounds (Feng et al., 2000); however, it failed to predict well for a few compounds with large vertical allometry such as diazepam and valproate. Recently, Mahmood (2000) suggested that unbound CL cannot be predicted any better than total clearance. Corrections either with MLP or BrW have been shown to be inappropriate if they are used indiscriminately, which led to the idea of ROE. This rule provides selection criteria for use of MLP or BrW, based on the values of the exponents obtained from simple allometry (Mahmood and Balian, 1996a). Although ROE has been shown to improve the prediction significantly compared with simple allometry, this method is still not satisfactory in predicting large vertical allometry. More recent studies (Nagilla and Ward, 2004) found that the corrections using MLP or BrW or the rule of exponents in allometric scaling did not result in significant improvements in predictions of human CL. Furthermore, they proposed that the monkey liver blood flow approach was superior to the rule of exponents. This controversy is currently not resolved (Mahmood, 2005; Nagilla and Ward, 2005).

The coefficients (*a*) of the power function have been considered important in determining the magnitude of CL, because the exponents (*b*) have been shown to be relatively constant, with a typical value close to 0.75 (Boxenbaum, 1982). Based upon analysis of more than 60 drugs, we have observed that the water-octanol partition coefficient (log P) and the ratio of unbound fraction (f_u) in plasma between rats and humans (Rf_u) may provide simple rules for anticipating the occurrence of large vertical allometry. Based upon these findings, therefore, we attempted to develop a new model for predicting human CL.

Materials and Methods

A literature search was performed to obtain animal data for allometric scaling of systemic CL (CL used in this article refers to systemic CL) and f_u ratio in rats and humans. Only data sets including at least three animal species were used for scaling. Coefficients and exponents were obtained by fitting body weight and CL, CL × MLP, or CL × BrW on a log-log scale according to the allometric equation: CL or CL × MLP or CL × BrW = $a \times W^b$. CL in humans was calculated by using the coefficients and exponents obtained and human body weight reported, or by assuming 70 kg (if weight was not reported in the publication). MLP was calculated by using MLP = $10.839 \cdot W^{0.636} \cdot BrW^{-0.225}$ (Boxenbaum, 1982). The rule of exponents was applied as described by Mahmood and Balian (1996a): 1) if the exponent from simple allometry is between 0.55 and 0.70, simple allometry is applied; 2) if the exponent is between 0.70 and 1.0, CL × MLP approach is applied; 3) if the exponent is greater than 1.0, CL × BrW approach is applied; 4) if the exponent is less than 0.50, simple allometry is applied since none of the approaches could improve the prediction. Predictability was assessed by percentage error (PE), which is $[(CL_{pred} - CL_{obs})/CL_{obs}] \times 100\%$ for over-prediction and, $[(CL_{obs} - CL_{pred})/CL_{pred}] \times 100\%$ for under-prediction. A power model is proposed,

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ABBREVIATIONS: CL, clearance; Rf_u, ratio of unbound fraction in plasma between rats and humans; MLP, maximum life-span potential; BrW, brain weight; ROE, rule of exponents; PE, percentage error; GV150526A, sodium 4,6-dichloro-3-[(*E*)-3-(*N*-phenyl)propenamide]indole-2-carboxylate; PK, pharmacokinetic.

TABLE 1

Comparison of predictability of human clearance obtained from simple allometry, the new model equations, and the rule of exponents

The order of drugs is arranged according to the ascending values of exponent b obtained from simple allometry.

Compounds	References	Rf_u	*a*	*b*	CL_{obs}	Simple Allometry		Equation 5		ROE	
						CL_{pred}	PE	CL_{pred}	PE	CL_{pred}	PE
			ml/min		*ml/min*	*ml/min*		*ml/min*		*ml/min*	
Indinavir	Lin et al., 1996	1.15	198.00	0.349	1325	872	−52	1757	33	872	−52
Remoxipride	Widman et al., 1993	2.94	36.50	0.362	119	170	43	232	95	170	43
CI-921	Paxton et al., 1990	9.73	13.74	0.439	188	89	−113	44	−332	89	−112
Ofloxacin	Nakamura et al., 1983; Okazaki et al., 1992; Kawakami et al., 1994	1.04	7.58	0.457	146	53	−178	154	5	53	−175
Dofetilide	Smith et al., 1992	0.98	19.20	0.462	105	136	30	330	214	136	30
Nilvadipine	Terakawa et al., 1987; Tokuma et al., 1987; Naritomi et al., 2001	0.90	32.07	0.514	560	285	−96	522	−7	285	−96
Enprofylline	Tsunekawa et al., 1992	0.46	6.34	0.526	315	59	−426	251	−25	59	−434
Ceftizoxime	Murakawa et al., 1980	0.99	11.24	0.563	126	123	−2	217	72	123	−2
Talsaclidine	Leusch et al., 2000	0.99	29.23	0.564	588	321	−82	452	−30	321	−83
Cefoperazone	Sawada et al., 1984	4.23	6.77	0.577	74	79	6	48	−54	79	7
Bosentan	Lave, et al., 1996a; Ubeaud et al., 1995	1.00	17.19	0.578	140	200	43	298	113	200	43
Antipyrine	Boxenbaum and Fertig, 1984; Chiou and Hsu, 1988	1.00	4.52	0.589	43	55	28	107	148	55	28
Moxifloxacin	Siefert et al., 1999	1.15	19.34	0.589	154	236	53	293	90	236	53
Tamsulosin	van Hoogdalem et al., 1997; Matsushima et al., 1998	20.00	61.00	0.594	48	761	1485	79	64	761	1485
Recainam	Scatina et al., 1990	1.02	2.20	0.601	30	28	−6	60	101	28	−7
Nicardipine	Higuchi et al., 1980; Naritomi et al., 2001	1.46	72.34	0.630	472	944	100	673	43	944	100
Cefmetazole	Murakawa et al., 1980; Komiya et al., 1981	3.73	12.80	0.633	129	188	46	86	−50	188	46
Ketamine	Bjorkman and Redke, 2000	0.93	120.50	0.635	1170	1787	53	1412	21	1787	53
Cefotetan	Komiya et al., 1981; Matsushita et al., 1990	7.78	7.13	0.639	30	108	256	31	4	108	260
Tolcapone	Lave et al., 1996b	1.00	7.23	0.646	118	113	−5	153	30	113	−4
Moxalactam	Sawada et al., 1984; Mahmood, 1999	1.28	4.97	0.651	93	79	−18	95	2	79	−18
Propranolol	Chiou and Hsu, 1988; McNamara et al., 1988	1.15	49.68	0.662	1050	827	−27	606	−73	827	−27
Sildenafil	Walker et al., 1999	1.25	28.95	0.679	420	518	23	375	−12	518	23
Tirilazad	Bombardt et al., 1994	2.17	26.50	0.693	580	503	−15	229	−153	503	−15
Ro 24-6173	Lave et al., 1997	1.30	68.82	0.716	840	1440	71	709	−19	477	−76
Sematilide	Hinderling et al., 1993	0.95	19.67	0.727	313	431	38	344	10	135	−132
Cefazolin	Lee et al., 1980; Sawada et al., 1984	0.56	4.79	0.733	53	108	104	174	229	47	−13
Mofarotene	Lave et al., 1997	1.00	11.50	0.733	770	259	−194	219	−252	84	−817
Diazepam	Laznicek et al., 1982; Mahmood and Balian, 1996a	5.00	37.57	0.737	27	860	3087	159	489	466	1626
Caffeine	Lave et al., 1997; Bonati et al., 1984	0.94	6.36	0.750	137	154	12	145	6	71	−93
Cefpiramide	Murakawa et al., 1980; Ohshima et al., 1991	14.59	4.70	0.755	19	6	553	14	−36	20	5
FCE22101	Efthymiopoulos et al., 1991	0.69	11.18	0.756	494	278	−79	285	−73	128	−286
NS-105	Kumagai et al., 1999; Mukai et al., 1999	1.00	7.90	0.759	141	199	41	164	16	155	10
Felbamate	Adusumalli et al., 1991; Palmer and McTavish, 1993	1.19	1.50	0.766	30	39	30	40	33	21	−43
Midazolam	Lave et al., 1997	1.00	52.30	0.785	798	1465	84	702	−14	290	−175
Dolasetron	Sanwald-Ducray and Dow, 1997	0.90	57.44	0.793	1232	1670	36	818	−51	907	−36
Mibefradil	Lave et al., 1997	2.00	66.88	0.804	532	2032	282	497	−7	642	21
Quinidine	Belpaire et al., 1977; Chiou and Hsu, 1988; Mahmood and Balian, 1996a	1.41	47.51	0.805	330	1452	340	500	52	285	−16
Sumatriptan	Cosson et al., 1997	1.01	31.71	0.808	1333	982	−35	474	−181	319	−318
Troglitazone	Izumi et al., 1996, 1997; Mahmood, 1999	0.98	12.44	0.810	411	383	0	236	−74	178	−131
Theophylline	Gaspari and Bonati, 1990; Lave et al., 1997	0.69	1.89	0.817	51	61	19	72	42	42	−21
Amlodipine	Stopher et al., 1988	3.00	29.00	0.821	490	949	94	191	−156	324	−51
DA-1131	Kim et al., 1998a,b	1.00	11.58	0.825	353	385	9	220	−61	104	−239
Alfentanil	Bjorkman and Redke, 2000	1.23	24.85	0.834	448	859	92	337	−33	253	−77
Norfloxacin	Nakamura et al., 1983; Mahmood and Balian, 1996a	1.02	90.02	0.836	1360	3139	131	1050	−29	912	−49
Meloxicam	Busch et al., 1998	0.60	0.35	0.855	12	13	13	22	84	8	−50
Methohexitone	Bjorkman and Redke, 2000	0.88	72.75	0.857	1000	2777	178	999	0	980	−2
Stavudine	Kaul et al., 1999	1.00	18.80	0.870	572	758	32	319	−79	466	−23
Amphotericin B	Hutchaleelaha et al., 1997; Robbie and Chiou, 1998	2.12	1.03	0.870	30	41	38	19	−57	17	−76
Fentanyl	Bjorkman and Redke, 2000	1.06	59.66	0.882	730	2525	246	743	2	384	−90
Propafenone	Puigdemont et al., 1991	0.33	71.07	0.890	1104	3117	182	2088	89	550	−101
SU 5416	Sukbuntherng et al., 2001	0.88	56.00	0.908	949	2652	179	816	−16	971	2
Ciprofloxacin	Siefert et al., 1986; Mahmood, 1999	1.10	17.65	0.927	423	1085	157	283	−50	270	−57
Valproate	Loscher, 1978; Loscher and Esenwein, 1978; Chiou and Hsu, 1988	7.04	3.66	0.944	7	202	2786	20	188	60	757
ACNU	Mitsuhashi et al., 1990	1.87	50.71	0.957	805	2950	266	423	−90	785	−3
Ethosuximide	Battino et al., 1995; Mahmood and Balian, 1996a	1.00	0.60	1.012	13	44	240	23	73	8	−63
Thiopentone	Bjorkman and Redke, 2000	0.57	3.67	1.059	215	330	53	140	−54	37	−481
AL01576	McNamara et al., 1988; Park et al., 1988; Brazzell et al., 1990	0.98	0.35	1.104	28	38	35	15	−86	30	7
Warfarin	Nagashima and Levy, 1969; von Oettingen et al., 1975	15.00	0.37	1.126	4	44	1006	2	−108	4	0
Ro25-6833	Richter et al., 1998	0.58	1.10	1.180	27	165	513	55	102	39	44
GV150526A	Iavarone et al., 1999	13.50	2.00	1.196	6	322	5266	8	28	132	2100
APE							323		78		185
S.D.							850		86		395

CI-921, 9-[[2-methoxy-4-[methylsulphonylamino]-phenyl]amino]-*N*,5-dimethyl-4-acridinecarboxamide; NS-105, (+)-5-oxo-*d*-prolinepiperidinamide monohydrate; SU 5416, semaxanib; ACNU, 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride; Ro 24-6173, an *N*-methyl-D-aspartate receptor antagonist; Ro25-6833, a cephalosporin; FCE22101, a

$$CL = \alpha \prod P_i^{\beta_i} \quad (1)$$

and transformed into

$$\text{Log } CL = \text{Log } \alpha + \sum \beta_i \cdot \text{Log } P_i \quad (2)$$

where P_i is the variable for a, b, Rf_u, or e^{ClogP} (exponential values of water-octanol-water partition coefficient, ClogP). The transformed model was screened by a backward step-wise procedure (P value entrance criterion at 0.1 and P value removal criteria at 0.2) to obtain parameters of statistical significance (Intercooled Stata 7.0, Stata Corporation, College Station, TX).

Results

The interest and rationale for developing a new allometric model equation was based on our previous findings that Rf_u, combined with ClogP, could be used to formulate rules to predict qualitatively the occurrence of large vertical allometry in predicting human CL (Tang and Mayersohn, 2005, in press). The current study was undertaken to create and test a model in which parameters such as Rf_u and ClogP, as well as coefficient a and exponent b from simple allometry, could potentially be useful to quantitatively predict human CL. ClogP was removed from the model since it did not add any statistical improvement. Coefficient a, exponent b, and Rf_u were found to be statistically significant with P values of <0.001, <0.05, and <0.001, respectively. The model equation incorporating these three variables was:

$$CL = 36.6 \cdot (\text{ml/min}) \cdot a^{0.82} \cdot b^{0.71} \cdot Rf_u^{-0.70} (R^2 = 0.82) \quad (3)$$

The exponential value of b (0.71) is close to that of a (0.82) and Rf_u (0.70). b is relatively constant and varies over a much narrower range ($\sim$ 0.35–1.20) than a (0.31–200) or Rf_u (0.33–20); therefore, b was not considered to be an important variable. Thus, a and Rf_u were used as the only variables to redevelop the model, which resulted in the simplified eq. 4,

$$CL = 33.35 \cdot (\text{ml/min}) \cdot a^{0.77} \cdot Rf_u^{-0.71} \quad (4)$$

which retained an R^2 of 0.81, indicating that the three-variable model does not improve the prediction performance. Values for CL increase with a, indicating that the coefficient a from simple allometry is a primary determinant of CL. In contrast, CL decreases when Rf_u increases due to the negative power of Rf_u. This inverse relationship makes sense in that a higher value for f_u in animals compared with humans may lead to an over-prediction of CL by simple allometry. The inverse functional relationship between f_u and CL predicted in humans, therefore, may correct the over-predictions caused by significant differences in f_u between animals and humans.

The exponents of a and Rf_u have very similar absolute values. Changing -0.71 to -0.77 for the exponent of the f_u ratio only slightly affects CL. For example, an Rf_u of 10 raised to the power -0.71 is 0.19, whereas 10 raised to the power -0.77 is 0.17. Most f_u ratios are smaller than 10; therefore, the equation was further simplified to

$$CL = 33.35 \cdot (\text{ml/min}) \cdot \left(\frac{a}{Rf_u}\right)^{0.77} \quad (5)$$

The term, a/Rf_u, could be referred as an "f_u-corrected a." The predictability of CL estimations for eq. 5, as well as for simple allometry and ROE, are given in Table 1. The significant improvement in prediction performance by the proposed model, compared with ROE, could be judged from three perspectives.

First, the average absolute values of percentage error by eq. 5, ROE, and simple allometry were 78%, 185%, and 323%, respectively. The significant improvement in prediction by the new model is

TABLE 2

A summary of outliers for predictions of human clearance (PEs greater than 200%) based on simple allometry, new model equation, and rule of exponents

Methods	APE	N (PE > 200%)	N (PE > 500%)	N (PE >1000%)
	%			
Simple allometry	323	11	6	5
Rule of exponents	185	11	6	3
Equation 5	78	6	1	0

APE, average of absolute percentage error.

Second, using the new model (e.g., eq. 5), only six compounds had percentage errors over 200%, with 548% for diazepam and 200 to 300% for the other five. In contrast, 11 compounds using the ROE method had prediction percentage errors greater than 200%, with 2100% for GV150526A, 1626% for diazepam, 1485% for tamsulosin, and 200 to 1000% for the other eight compounds (Table 2). Therefore, the new model predicted the large vertical allometry with greater success compared with ROE.

Comparisons of the predictability of human CL from simple allometry with the new model (eq. 5) and ROE may be visualized in Fig. 1

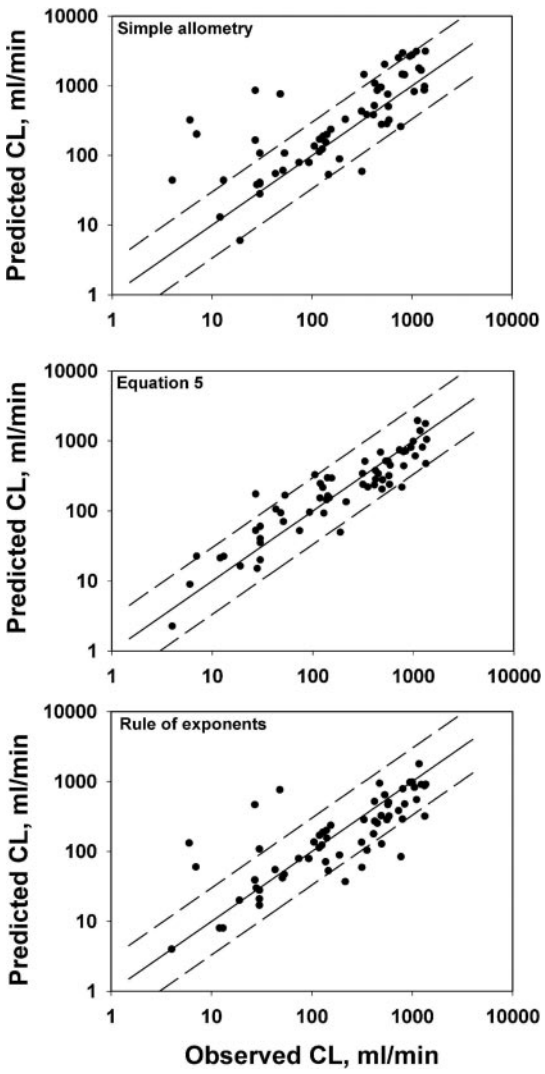

FIG. 1. Predicted human clearance as a function of observed human clearance. Predicted values are based upon simple allometry (top), the new model equation derived here (eq. 5; middle) and the rule of exponents (bottom). The solid lines are the lines of

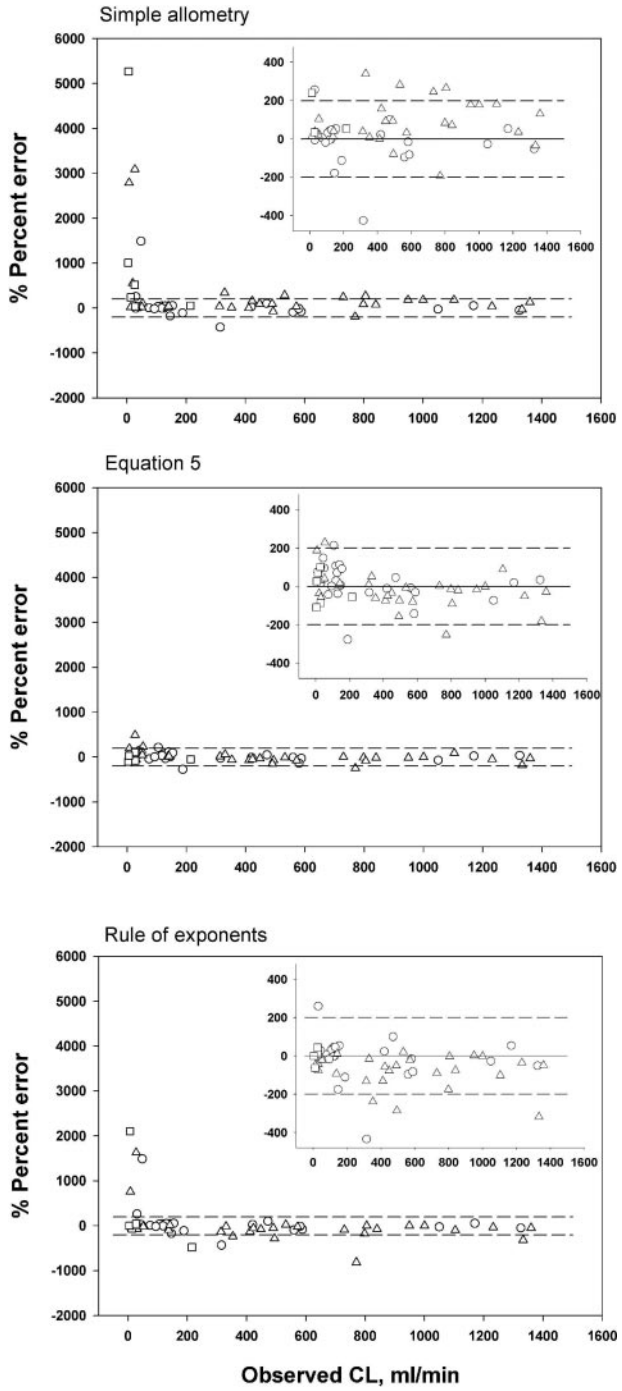

FIG. 2. Percentage error in prediction of human clearance as a function of observed human clearance. Percentage errors are from predictions based upon simple allometry (top), the new model eq. 5 (middle), and the rule of exponents (bottom). The inset plots are limited to 400% error, which encompasses most of the error range. The solid lines indicate 0% error. The dashed lines indicate the range associated with 200% error. Symbols: simple allometric slope values less than 0.7 (circle), less than 0.7–1.0 (triangle), or greater than 1.0 (rectangle).

and Fig. 2. The dashed line in the graphs represents a 200% error range. Simple allometry results in substantial over-prediction of human CL for many compounds (especially those with low CL). The ROE method considerably reduces that error, whereas it still retains a few large over-predictions and leads to biased under-predictions. The under-predictions by the ROE method are primarily the result of

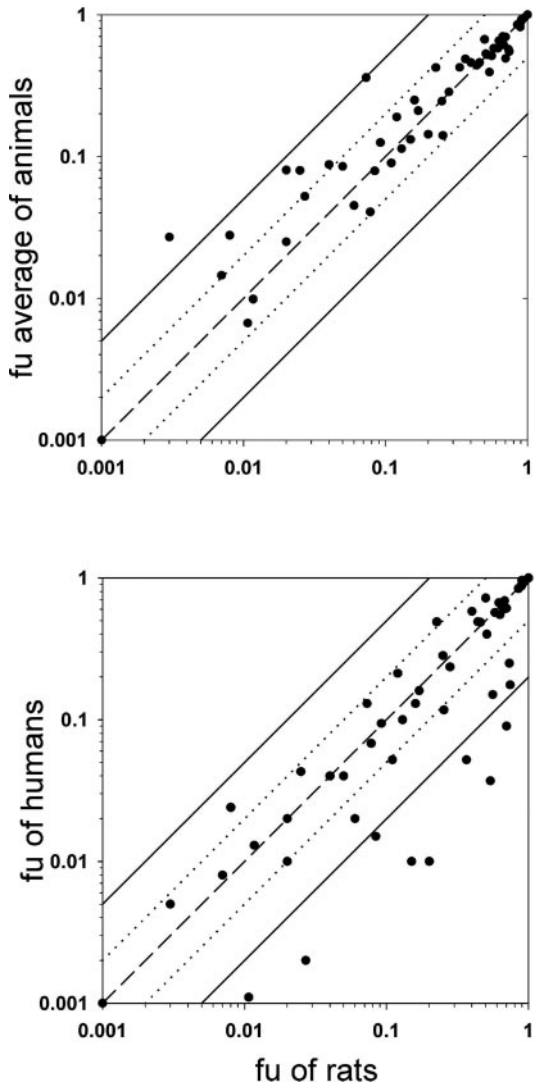

FIG. 3. Unbound fraction of drug in plasma (f_u) for the average in all animal species (top) and in humans (bottom) as a function of f_u in rats for 61 compounds. The average f_u values in animals are based on at least two animal species including rats. The solid lines indicate the lines of 5-fold or 0.2-fold. The dotted lines indicate the lines of 2-fold or 0.5-fold. The dashed lines indicate the lines of identity.

exponents greater than 0.70. In contrast, the new model equation proposed here results in more accurate predictions of human CL and a more random pattern of errors.

Discussion

The use of f_u ratio between rats and humans, rather than between all animals and humans, was based on our observation that the f_u in rats is representative of the average f_u in animals (Fig.3). In contrast, many significant differences between f_u in rats and f_u in humans were observed (Fig. 3). One question could be raised concerning why scaling by the unbound CL approach did not provide stable and good predictability, because it appears that correcting CL by f_u in each animal species would be more favorable than just considering only rats and humans. One possible explanation could be attributed to the serious error underlying data fitting to the power function (Smith, 1984) and the considerable measurement error of f_u, especially for highly plasma-bound compounds. When three or more animal species are included for scaling unbound CL, the same number of f_u variables

greater error in predicting human values than what is generated from the error noted in only one species, the rat, in the new proposed model. Here is an example to visualize this concept. Suppose three species, mouse (0.03 kg), rat (0.25 kg), and dog (15 kg), are used for allometric scaling of unbound CL. The final predicted CL in humans by allometry can be expressed as:

$$CL_{predicted} = A \cdot (f_u^{mouse})^{0.36} \cdot (f_u^{rat})^{-0.17} \cdot (f_u^{dog})^{-1.19} \cdot (f_u^{human})^{1.0} \quad (6)$$

where A is a function of CL observed in each animal species and the body weight of animals (derivation under *Appendix*). The new model can be expressed as:

$$CL_{predicted} = B \cdot (f_u^{rat})^{-0.77} \cdot (f_u^{human})^{0.77} \quad (7)$$

where B is not equal to A, but is also a function of CL observed in each animal species and the body weight of animals. It is obvious that the correction of f_u in each species incorporates more variance by introducing more f_u variables compared with both simple allometry and the new model.

Certainly, the new model is empirical, just as are all of the other approaches. No solid physiological or biochemical basis could be offered at this time. The model proposed here does not consider many other potential types of useful information such as in vitro metabolic differences across species, which may account for deviations in predictions. Therefore, the empirical model that has been proposed should be expected, in practice, to result in errors in prediction, such as when a significant metabolic/elimination difference is seen across the species examined. Nevertheless, the new model was shown to be simple, reasonable, and more predictive than the currently available approaches. In particular, the new model significantly improves for the first time the prediction of the occurrence of large vertical allometry noted in humans.

In summary, a novel and simple model, incorporating a and the f_u ratio between rats and humans, has been proposed and shown to provide a better predictability than the currently available allometric techniques in estimating values of CL in humans. Most important, it significantly improves the prediction of large vertical allometry.[2]

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Appendix: Derivation of Equation 5

Part I: Derivation of the Function Relating Predicted PK Parameters in Humans ($P_{predicted}$) to Animal Body Weights (W) and Observed Animal PK Parameters (P_i)

The log-log transformation of $P = a \cdot W^b$ gives

$$\log P = \log a + b \cdot \log W \quad (A1)$$

Let

$$Y = \log P; X = \log W; a = 10^{\alpha}; b = \beta$$

Then, eq. A1 can be simplified to

$$Y = \alpha + \beta \cdot X \quad (A2)$$

Suppose n different animal species are used for allometric scaling. Therefore, there are n sets of (X, Y) data to fit using linear regression. Based on the method of least squares for linear regression, α and β can be calculated as

$$\beta = \frac{\sum_{i=1}^{n} (X_i - \bar{X})(Y_i - \bar{Y})}{\sum_{i=1}^{n} (X_i - \bar{X})^2} \quad (A3)$$

$$\alpha = \bar{Y} - \beta \cdot \bar{X} \quad (A4)$$

Substituting $Y = \log P$, $X = \log W$ into eqs. A3 and A4, and further substituting α and β into $a = 10^{\alpha}$, $b = \beta$, expressions of a and b are obtained as

$$a = \prod_{i=1}^{n} P_i^{A_i} \quad (A5)$$

$$b = \sum_{i=1}^{n} B_i \cdot \log P_i \quad (A6)$$

where

$$A_i = \frac{1}{n}\left(1 - B_i \cdot \log \prod_{j=1}^{n} W_j\right) \quad (A7)$$

$$B_i = \frac{1}{n} \cdot \frac{\log \frac{W_i^{n-1}}{\prod_{\substack{k=1 \\ k \neq i}}^{n} W_k}}{\sum_{k=1}^{n} \left(\log W_k - \frac{\log \prod_{l=1}^{n} W_l}{n}\right)^2} \quad (A8)$$

By assuming a human body weight of 70 kg, the predicted P in humans is obtained from

$$P_{predicted} = a \cdot 70^b = \prod_{i=1}^{n} P_i^{(A_i + 1.845 B_i)} \quad (A9)$$

where $P_{predicted}$ is the predicted PK parameter in humans and P_i is the measured PK parameter in an animal species,

$$A_i = \frac{1}{n}\left(1 - B_i \cdot \log \prod_{j=1}^{n} W_j\right) \quad (A10)$$

[2] The proposed model (eq. 5) was tested using one example of large vertical allometry (reboxetine), whose data were available to the authors during the revision of the manuscript. We predicted an Rf_u greater than 5 for reboxetine. The data kindly provided by one of the reviewers (courtesy of Pfizer, Inc.) showed f_u values of 0.17 and 0.02 in rats and humans, respectively, which translate to an Rf_u of 8.5. Prediction of human CL based upon eq. 5 resulted in a PE of 104%, compared with 1395% and 804% based upon simple allometry and the ROE

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