Allometric Pharmacokinetic Scaling: Towards the Prediction of Human Oral Pharmacokinetics

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Purpose. To evaluate (1) allometric scaling of systemic clearance (CL) using unbound drug concentration, (2) the potential usage of brain weight (BRW) correction in allometric scaling of both CL and oral clearance (CL/F).

Methods. Human clearance was predicted allometrically ($CLu = a \cdot W^{biv}$) using unbound plasma concentration for eight Parke-Davis compounds and 29 drugs from literature sources. When the exponent b_{iv} was higher than 0.85, BRW was incorporated into the allometric relationship ($CLu*BRW = a \cdot W^{biv}$). This approach was also applied to the prediction of CLu/F for 10 Parke-Davis compounds. Human oral $t^1/_2$, Cmax, AUC, and bioavailability were estimated based on allometrically predicted pharmacokinetic (PK) parameters.

Results. Human CL and CL/F were more accurately estimated using unbound drug concentration and the prediction was further improved when BRW was incorporated into the allometric relationship. For Parke-Davis compounds, the predicted human CL and CL/F were within 50–200% and 50–220% of the actual values, respectively. The estimated human oral $t^1/_2$, Cmax, and AUC were within 82–220%, 56–240%, and 73–190% of the actual values for all 7 compounds, suggesting that human oral PK parameters of those drugs could be reasonably predicted from animal data.

Conclusions. Results from the retrospective analysis indicate that allometric scaling of free concentration could be applied to orally administered drugs to gain knowledge of drug disposition in man, and to help decision-making at early stages of drug development.

KEY WORDS: allometric scaling; interspecies scaling; pharmacokinetics.

INTRODUCTION

In order to improve and expedite drug selection and development, many industrial pharmacokineticists are seeking tools to help predicting human pharmacokinetic parameters. Allometric scaling is grounded on the similarity of anatomical, physiological, and biochemical variables in mammals. Although empirical, the approach is widely used to extrapolate from animal to human. Correlation between pharmacokinetic parameters (e.g. clearance, volume of distribution, half-life) and body weight (W) was reported for many intravenously (IV) administrated drugs (1–11). For some hepatically oxidized drugs, over-estimation of human clearance was reported, and Boxenbaum suggested incorporating maximum life span (MLP) into the allometric equation ($CL = a \cdot W^b/MLP$) for correction since longevity is frequently inversely correlated with hepatic P450 drug oxidation rates. This investigator corrected the overestimation of hepatic intrinsic clearance (CLint) for several drugs by incorporating MLP into the conventional allometric relationship (1–4). Boxenbaum also explored the possibility of using brain weight (BRW) as a correction factor ($CL = a \cdot W^b \cdot BRW^c$). MLP is highly correlated to BRW and W as $MLP = 10.839 \cdot (BRW^{0.636})(W)^{-0.225}$, where MLP is in years. Applying the simple allometric equation to animal data, human MLP and BRW predictions are approximately 4 and 9 times less than observed values, suggesting these two variables may be used to correct overestimation of clearance. In addition to CLint, scaling using unbound or total plasma clearance was evaluated by other scientists. Work from Chiou's group shown that human CL would be more accurately predicted using unbound plasma CL (7, 10–11). Mahmood and Balian analyzed several series of drugs using total plasma concentration and proposed three approaches for human CL prediction based on the exponent b in the allometric equation $CL = a \cdot W^b$ (8–9). They suggested incorporating MLP into the allometric relationship ($CL \cdot MLP = a \cdot W^b$) when exponent b is between 0.71 to 1.0 (0.75–0.90 from analysis of 9 anti-cancer drugs), and to correct with BRW ($CL \cdot BRW = a \cdot W^b$) when b is higher than 0.90 or 1.0. Our current work is a continuation of this effort.

In this paper, human systemic CL was predicted using unbound drug concentration and BRW was incorporated as a correction factor when exponent b_{iv} was higher than 0.85. Eight Parke-Davis compounds (Fig. 1) and 26 literature drugs were evaluated, and the approach was also applied to the prediction of human CL/F for orally administered Parke-Davis compounds (Fig. 1). Drugs tested in this study are small molecules eliminated hepatically, renally, or with mixed functions. For selected Parke-Davis oral drugs, human half-life ($t^1/_2$), Cmax (maximum drug concentration), AUC (area under the concentration-time curve), and bioavailability (%F) were estimated based on allometrically predicted CL, CL/F, and volume of distribution and compared with the actual human parameters.

MATERIALS AND METHODS

Allometric Scaling of CL and CL/F

Eqs. 1–2 were used for the scaling of systemic CLu for IV route. If the exponent b_{iv} was less than or equal to 0.85, no correction was needed and human CLu was predicted by Eq. 1.

$$CLu = a_{iv} \cdot W^{b_{iv}} \quad (1)$$

If the exponent b_{iv} in equation 1 was greater than 0.85, *CLu* values were corrected with BRW by eq. 2.

$$CLu \cdot BRW = a_{iv} \cdot W^{b_{iv}} \quad (2)$$

For orally administered drugs, equations 3–4 were applied to the interspecies scaling of *CLu/F* based on the allometric exponent b_{iv} obtained from Eq. 1. If the exponent b_{iv} was less

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ABBREVIATIONS: CL, systemic clearance; CL/F, extravascular (oral) clearance; F, absolute bioavailability; *fu*, unbound fraction; CLu, unbound systemic clearance; CLu/F, unbound oral clearance; V1(u)/F, unbound volume of distribution of central compartment for oral route; $t^1/_2$, elimination half life; Cmax, maximum plasma concentration; AUC, area under the concentration-time curve; MLP, maximum life span; BRW, brain weight.

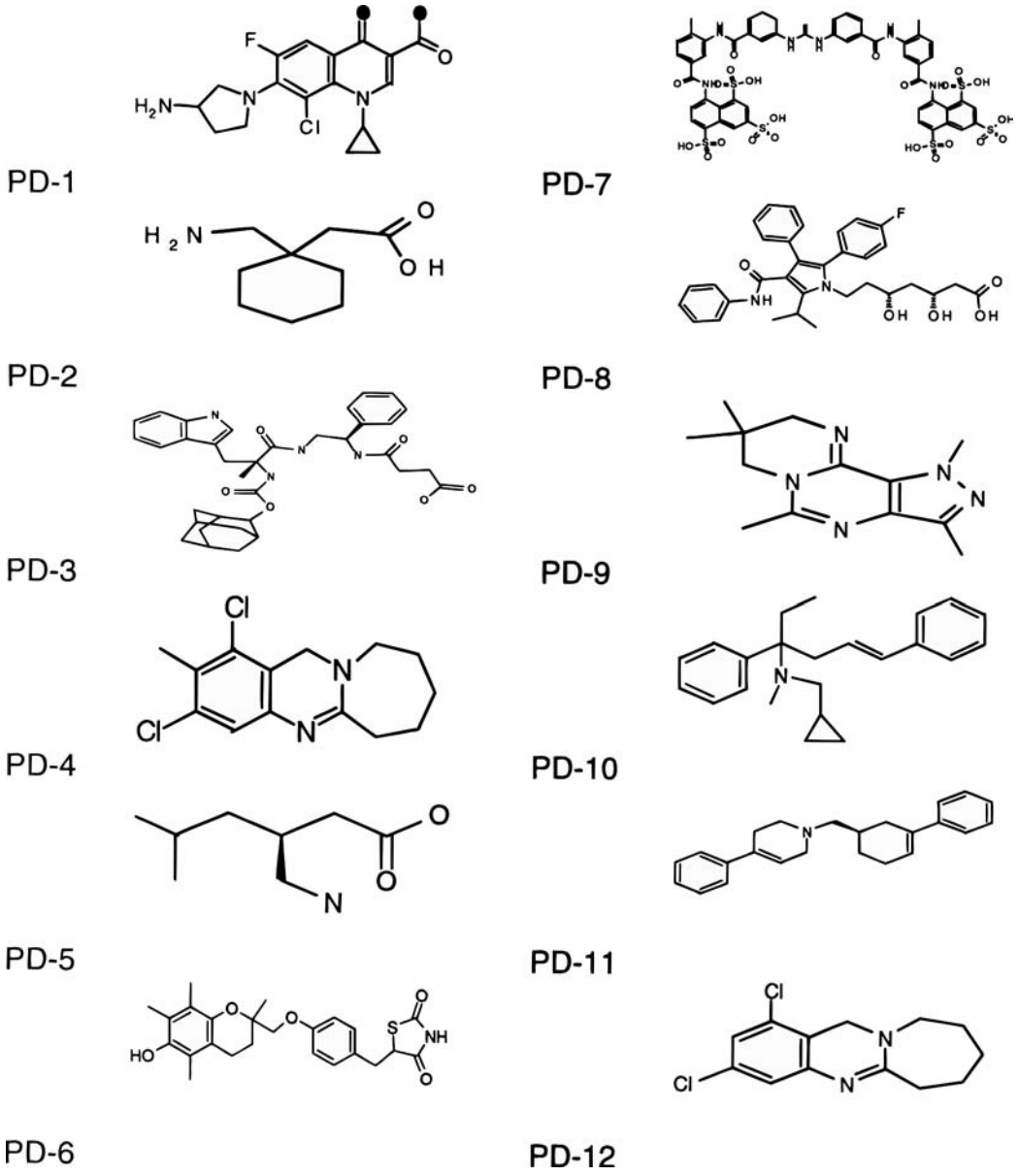

Fig. 1. Chemical structure for Parke-Davis compounds.

than or equal to 0.85, no correction was used and human *CLu*/*F* was predicted by Eq. 3. If the exponent b_{iv} was greater than 0.85, *CLu*/*F* values were calculated by equations 4 with BRW correction.

$$CLu/F = a_{po} \cdot W^{b_{po}} \quad (3)$$

$$(CLu/F) \cdot BRW = a_{po} \cdot W^{b_{po}} \quad (4)$$

Human CL or CL/F was calculated by Eqs. 5 or 6, where *fu* is the unbound fraction in plasma.

$$CL = CLu \cdot fu \quad (5)$$

$$CL/F = CLu/F \cdot fu \quad (6)$$

Estimation of Human Oral Pharmacokinetic Parameters for Parke-Davis Compounds

Human plasma *AUC* and oral bioavailability (%*F*) were estimated using equations 7–8.

$$AUC = Dose/(CL/F) \quad (7)$$

$$\%F = (CL) \cdot 100\%/(CL/F) \quad (8)$$

Human plasma Cmax, elimination $t^1/_2$, and concentration-time profile were estimated with WinNonlin based on allometrically predicted parameters. Central volume of distribution *V*1/*F* was estimated by equations 9–10.

$$V1(u)/F = a \cdot W^b \quad (9)$$

$$V1/F = V1(u)/F \cdot fu \quad (10)$$

When a concentration-time profile was described by a one-compartment model with first-order of absorption, the mean absorption rate constant *K*01 from animals was used as initial estimate for human *K*01. When a concentration-time profile was best described by a one-compartment or 2-compartment model with zero order of absorption, mean tmax (time to reach

maximum plasma concentration) obtained from animals was used as initial estimation of zero-order absorption time (T) for the calculation of zero order absorption rate $K0$ ($K0 = Dose/T$).

Statistical Analysis

To evaluate the various methods used for the prediction of clearance and other parameters, average-fold error was calculated with equation 11 (12).

$$\text{Average-fold error} = 10^{\Sigma|\log(\text{predicted}/actual)|/N} \quad (11)$$

This approach prohibited poor over-estimations being canceled out by poor under-estimations; under-estimations were of equal value to over-predictions. It also did not allow any single outlier prediction from biasing conclusions concerning a particular prediction method. A method that predicted all actual values perfectly would have a value of 1; one that made predictions that were on average 2-fold off (100% above or 50% below) would have a value of 2 and so forth.

RESULTS AND DISCUSSION

Allometric Scaling of Systemic CL

Eight Parke-Davis compounds and twenty six literature drugs were tested and the predicted human systemic clearance using unbound concentration are summarized in Table 1 and 2. Comparison of the predicted versus the actual human CL for all 37 drugs using total or free drug concentration is presented in Figs. 2a–2b. In general, human CL is more accurately predicted using the unbound drug concentration (2b) with average-fold error reduced from 2.8 (2a) to 2.3 (2b). For drugs with significant cross species variation in protein binding like tamsulosin, remoxipride, cefotetan, and RO 25-6833, the ratio of $CL_{predict}/CL_{actual}$ reduced from 3.3–15.8 to 0.99–2.0 using unbound concentrations. Prediction was not improved for drugs with similar *fu* (unbound fraction) across species or with *fu* less than 5.0–10% since the accuracy of *fu* measurement may be limited by analytical sensitivity.

Even using unbound concentration, human clearance values were still significantly over-estimated for eight drugs in Tables 1 and 2 with the ratio of $CL_{predict}/CL_{actual}$ ranging from 3.6–32.9. The authors noted that over-estimation may happen to drugs with either high or low CL values. However, significant over-estimation usually occurred to drugs with an allometric exponent b_{iv} higher than 0.85 in our analysis. When BRW correction was applied (equation 2) to drugs with b_{iv} higher than 0.85, the correlation between the predicted and the actual human CL was greatly improved with average-fold error decreased from 2.3 (1b) to 1.7 (1c). For seven out of the eight drugs with significant over-estimation, the ratio of $CL_{predict}/CL_{actual}$ reduced to 0.5–1.9. The prediction for diazepam was a challenge. Human systemic CL and *fu* values were reported as 0.35 ml/min/kg and 3.2% (8) or 0.38 ml/min/kg and 1.3% (23) from two separate publications, and the predicted human CL would be 3.8-fold and 1.3-fold of the actual value, respectively. The above inconsistency again suggests that human clearance prediction could be limited by the accuracy of protein binding determination when *fu* value is lower than 5–10%.

It is interesting to see that over-estimation only occurred to drugs mainly metabolically eliminated. As listed in Table 2, cefedizime and cyprofloxacin are drugs predominantly eliminated in urine as unchanged. Although the allometric exponent b_{iv} was approximately 1.0 for both drugs, no over-estimation was observed and the estimated human CL was within 2-fold

Table 1. Predicted Human Clearance (CL or CL/F) Using Unbound Concentration for Parke-Davis Compounds

				Human clearance (ml/min/kg)				
				Predicted			Ratio (predicted/actual)	
	Route	Fu%	Exponent	No correction	BRW correction	Actual	No correction	BRW correction
PD-1	IV	49	0.51	2.42		3.28	0.74	
PD-2	IV	100	0.63	1.05		1.61	0.65	
PD-3	IV	3.7	0.78	16.5		10.8	1.52	
PD-4	IV	45	0.78	38.9		34.6	1.1	
PD-5	IV	100	0.81	1.01		1.04	0.97	
PD-6	IV	0.10	0.81	5.7		4.12	1.4	
PD-7	IV	0.23	0.97	0.024	0.0032	0.0043	5.6	0.74
PD-8	IV	16	1.1	49.0	12.4	8.5	5.7	1.5
PD-1	PO	49	0.51[a]	12.8		7.09	1.8	
PD-2	PO	100	0.63[a]	2.27		2.84	0.80	
PD-4	PO	45	0.78[a]	246		289	0.85	
PD-5	PO	100	0.81[a]	0.83		1.01	0.82	
PD-6	PO	0.10	0.81[a]	11.3		13.1	0.86	
PD-10	PO	0.10	0.56[a]	92.6		66.7	1.4	
PD-12	PO	2.6	084[a]	900		1246	0.72	
PD-8	PO	16	1.1[a]	618	155	71.1	8.7	2.2
PD-9	PO	0.35	0.98[a]	29.5	8.36	7.26	4.1	1.1
PD-11	PO	0.10	0.87[a]	575	290	491	1.2	0.59

[a] Exponent was calculated from animal systemic CL data, which was used to decide if BRW correction is needed. The actual human CuL/F values were calculated from actual animal CLu/F as shown in Fig. 5.

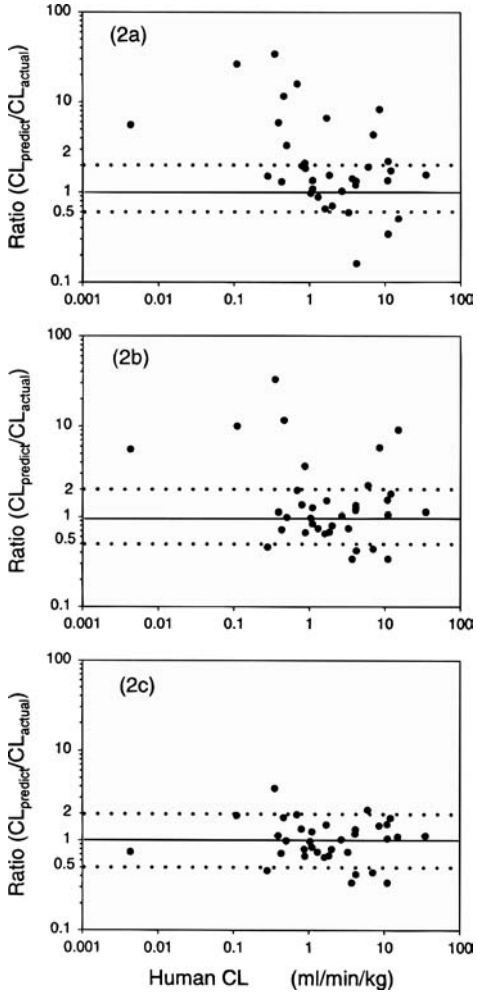

Fig. 2. Plots of the ratio of $CL_{predicted}/CL_{actual}$ versus the actual human systemic clearance (*CL*) for 37 drugs using total drug concentration (2a), unbound drug concentration (2b), with brain weight (BRW) correction for drugs with allometric exponent b_{iv} larger than 0.85 (2c). The solid line represents the line of identity. The two dotted lines above and below represent the 2-fold over-estimation and 2-fold under-estimation of human clearance, respectively.

of the actual value without BRW correction. The allometric exponent b_{iv} is generally lower than 0.85 for other drugs eliminated renally. The selected value of "0.85" is very close to the exponent "0.849" in the allometric equation of liver weight (Liver weight = $0.037 \cdot B^{0.849}$) (1). It is known that cytochrome P-450 (mixed function oxidase) enzyme system is involved in most drug-metabolizing activity and total hepatic cytochrome P-450 content correlates with liver weight. This suggests that if metabolic clearance of a drug is proportional to total P-450 content and liver weight, the exponent b_{iv} in Eq. 1 would be close to 0.85. If the exponent b_{iv} is larger than 0.85, systemic clearance appears to increase more than proportionally to liver weight in animals, and an additional physiological parameter (e.g. BRW) is needed to correct the over-estimation of human CL.

The authors would also like to point out that incorporation of BRW is still an empirical approach, although it is supported by the inverse relationship between longevity and liver P450 oxidation rate. BRW correction could not help if human CL was under-estimated. As listed in Table 2, the predicted human CL of four drugs was below 50% (34%–46%) of the actual value. Allometric scaling was also challenged by drugs mainly excreted in bile as unchanged (26). In general, mice, rats and dogs are good biliary excreters, while rabbits, guinea pigs, monkeys, and humans are relatively poor biliary excreters (27). Hepatic blood flow and bile flow does not seem to correlate with the biliary excretion of drugs. The hepato-biliary excretion of many compounds is mediated by primary active transports, and human clearance could not be predicted using allometric scaling.

Another method evaluated in this work was a direct correlation of CLu between single animal species and human. This approach was investigated previously by Chiou's group and a good correlation with a R^2 value of 0.94 has been reported for 15 drugs using unbound CL (11). We also found good correlation between human and monkey (3c) or rat (3a) with correlation coefficient (R^2) of 0.93 and 0.89 respectively. Comparison of the predicted versus the actual human CL is presented in Fig. 3 and human CLu was predicted by the following equation,

$$\text{Log}(\text{CLu}_{\text{human}}) = m \cdot \text{Log}(\text{CLu}_{\text{animal}}) + n$$

where m and n were the slope and intercept from linear regression of each data set. Although monkey data were available for only 16 drugs, the plot in Fig. 3c suggests that monkey may be the species closest to human with 75% of the predicted within 2-fold and 100% predicted within 3-fold of the actual human CLu. The next animal species is rat (3a) with 63% of the predicted within 2-fold of the actual human CL. Data points were more scattered when rabbit (3b) or dog (3d) CLu was used for human estimation. The above results suggest that direct correlation approach could be a useful alternative for human CL prediction. As for allometric scaling, if the drug could only be tested in 2–3 species due to resource limitation, rat and monkey may be considered first, while dog is the third species of selection. Rat is reported as a good model for studying absorption in human (28).

Prediction of Human Oral Pharmacokinetic Parameters

The BRW correction strategy was also applied to the prediction of orally clearance for Parke-Davis compounds with allometric exponent b_{iv} higher than 0.85. (Table 1, Fig. 4). We suggest using the exponent b_{iv} instead of b_{po} to decide if BRW correction is needed since the allometric exponent b_{po} may vary depending on the F value. Human CL/F was more accurately predicted after BRW correction (Table 1) with the predicted within 50–220% of the actual values.

Most drugs are developed for oral therapy, and an important goal for industrial pharmacokineticists is to predict oral dosing regimen (t1/2) and exposure (Cmax and AUC) prior to the first dose in human. These parameters are also important for the interpretation of therapeutic effects, adverse events, and potential drug accumulation after repeated dosing. The predicted CL, CL/F, and V1/F (Fig. 5) were further used for estimation of human t1/2, Cmax, AUC, and %F using WinNONLIN program. The estimated human t1/2, Cmax and AUC are within 82–220%, 56–240% and 73–190% of the actual value for seven Parke-Davis compounds (Table 3, Fig. 6), suggesting that oral dose regimen, concentration-time profile and drug

Table 2. Predicted Human Systemic Clearance (CL) for 26 Literature Drugs Using Unbound Concentrations

Drug	fu(%)	Exponent		R[a]		CL-actual	Ratio (predicted/actual)		Reference
		CL/fu	CL	CL/fu	CL	(ml/min/kg)	No correction	BRW correction[b]	(species used)
Bosetan	2.0	0.39	0.56	0.41	0.15	3.7	0.34		17 (Ms, Mm, R, Rb, D, H)
Remoxipride	27	0.52	0.51	0.92	0.88	1.7	1.5		20 (Ms, R, D, H)
Ceftizoxime	72	0.55	0.54	1.0	1.0	1.1	1.2		8 (Ms, R, D, H)
Caffeine	96	0.58	0.58	0.99	0.99	2.0	0.80		17 (R, Rb, D, H)
Mibefradil	1.0	0.58	0.80	0.99	0.99	7.0	0.44		17 (Mm, Rb, D, H)
Enprofylline	49	0.60	0.54	0.84	0.75	4.2	0.42		18 (Ms, R, G, Rb, D, H)
Cefpiramide	3.7	0.64	0.44	0.97	0.52	0.28	0.46		24 (Ms, R, Rb, Mk, D, H)
Tolcopone	0.1	0.65	0.65	0.86	0.86	2.7	1.0		17 (R, Rb, D, H)
Moxalactam	40	0.67	0.65	0.96	0.98	1.3	0.74		8 (Ms, Rb, Mk, D, H)
Sematilide	96	0.70	0.71	0.98	0.99	4.1	1.2		19 (Ms, R, Rb, Mk, D, H)
Cefametazole	15	0.71	0.63	1.0	1.0	1.84	0.68		19 (R, D, H)
Cefotetan	9.0	0.73	0.64	0.91	0.90	0.50	0.99		8 (Ms, R, Rb, Mk, D, H)
Mofarotene	0.1	0.73	0.73	0.98	0.89	11.0	0.34		8 (Ms, R, Rb, Mk, D, H)
Cefoperazone	18	0.74	0.58	1.0	1.0	1.1	0.84		17 (Ms, R, D, H)
Cefazolin	13	0.74	0.73	0.95	0.75	0.88	0.70		8 (Ms, R, Rb, Mk, D, H)
Cefodizime	12	0.99	1.00	0.99	0.92	0.79	1.3		14 (Ms, R, Rb, Mk, D, H)
Cyprofloxacin	60	1.00	0.94	0.91	0.93	6.0	2.2		21, 22 (R, Mk, C, P, H)
Tamsulosin	1.0	0.74	0.59	1.00	0.99	0.69	1.9		12 (R, Rb, D, H)
RO 24-6173	10	0.76	0.72	1.00	0.99	12.0	1.8		17 (R, Rb, D, H)
RO 25-6833	4.3	0.78	1.18	0.99	0.96	0.39	1.1		13 (R, Mk, D, H)
AmphotericinB	5.2	0.84	0.85	0.99	0.99	0.43	0.72		10, 16 (Ms, R, Rb, D, H)
Propranolol	8.4	0.92	0.61	0.98	0.98	15.0	9.0	1.1	8 (R, Rb, D, H)
Antipyrine	100	0.93	0.93	1.00	0.97	0.46	11.5	1.8	17 (R, Rb, D, H)
Theophylline	58	0.96	0.91	0.94	0.88	0.87	3.6	0.80	8 (R, G, Rb, D, H)
Diazepam[c]	3.2	1.00	0.73	0.99	0.95	0.35	32.9	3.8	8 (R, Rb, D, H)
Valproate	5.2	1.16	0.95	0.99	1.0	0.11	9.9	1.9	12 (Ms, R, D, H)
Midazolam	4.0	2.15	1.47	1.00	0.99	11.0	12.3	2.0	17 (Rb, D, P, H)

[a] Correlation coefficient R for the linear regression of allometric equation CL = a + b* Log (body weight).
[b] Brain weight (BRW) justification was applied for 7 drugs with allometric exponent higher than 0.85.
[c] The ratio would be 1.3 if CL of 0.38 ml/min/kg and fu of 1.3% from reference 39 are used.

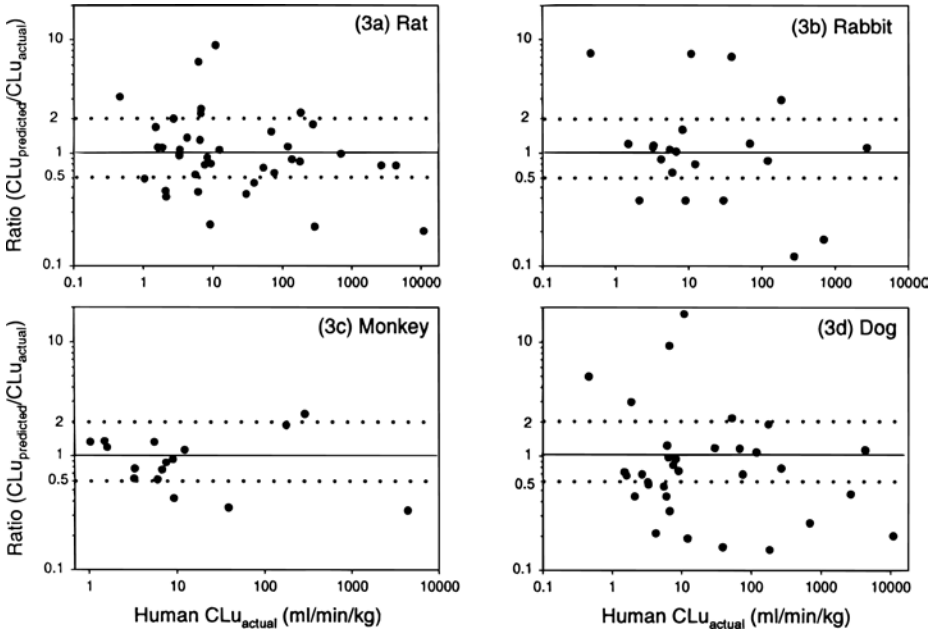

Fig. 3. Plots of the ratio of $CL_{predicted}/CL_{actual}$ versus the actual human systemic clearance (*CLu*) using rat (3a), rabbit (3b), monkey (3c), and dog (3d) data. Human *CLu* was predicted based on the slope and intercept in Figure 4. The solid line represents the line of identity. The two dotted lines above and below represent the 2-fold over-estimation and 2-fold under-estimation of human clearance, respectively.

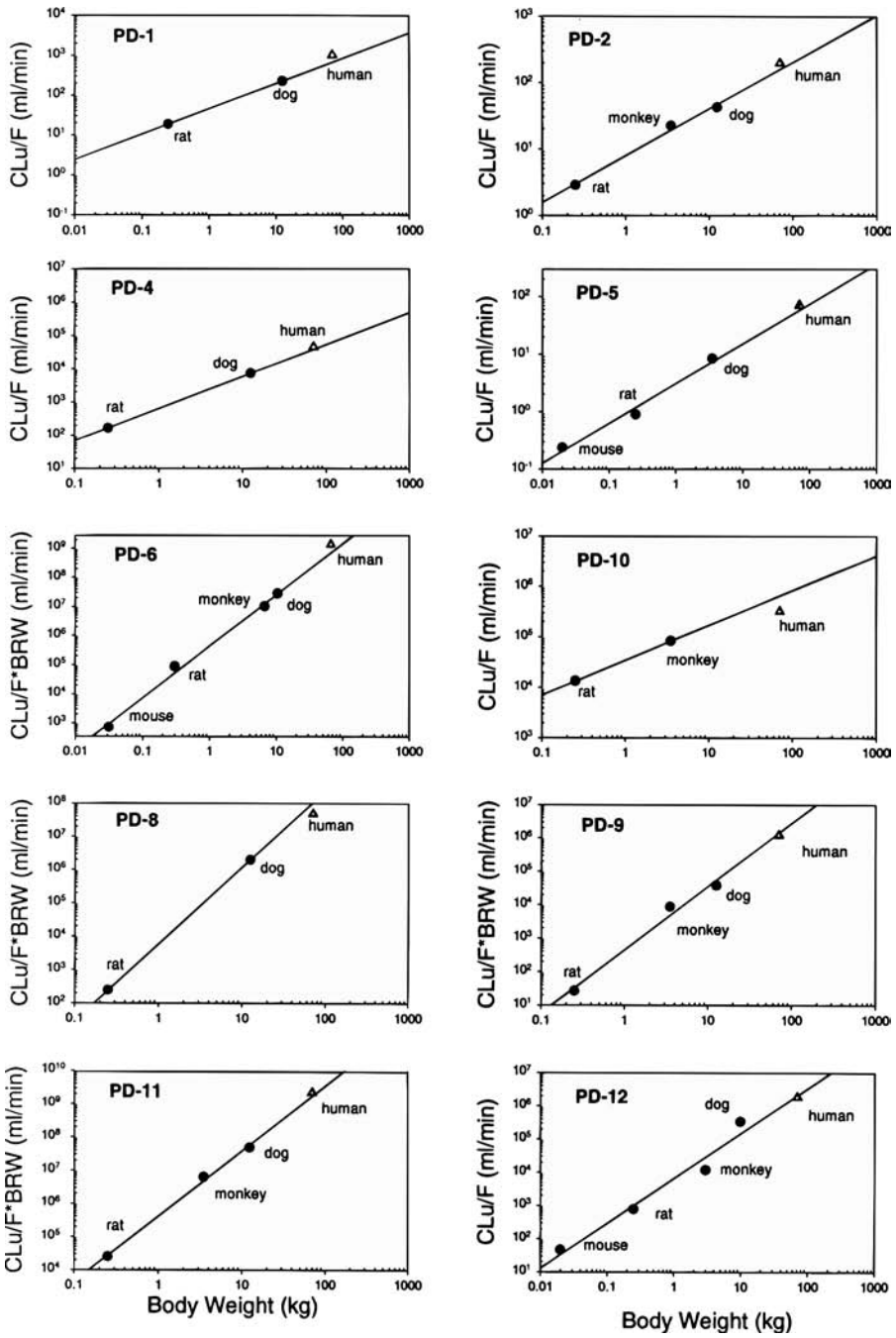

Fig. 4. Plots of the unbound *CLu/F* versus body weight for orally dosed Parke-Davis compounds.

exposure could be reasonably predicted by our approach. The concentration-time profile of PD-10 was best described by a 2-compartmental model with zero-order of absorption as described in equation 8. Good correlation was achieved between the predicted and the actual pharmacokinetic parameters for PD-10 with mean P/A (predicted/actual) ratio of 1.2, 0.65 and 0.75 for t1/2, Cmax and AUC, respectively (Table 3). Our results are consistent with the previous report from the scaling of ceftizoxime by Mordenti (15), and further suggest that the distribution and elimination rate constants could be scaled-up directly in allometric analysis.

The predicted bioavailability (%F) of four compounds was compared with the actual value yielding P/A ratio of 75–150%. Those three compounds are generally well absorbed and have shown moderate variation in bioavailability across species. If the bioavailability across species is significantly variable due to species differences in absorption and/or metabolism, the data need to be evaluated more carefully with additional information of in vitro permeability and/or in vitro metabolic clearance. In recent years, scientists have been exploring the possibility to predict the rate of absorption and clearance in human using in vitro models or by the integration of in vitro and in vivo data

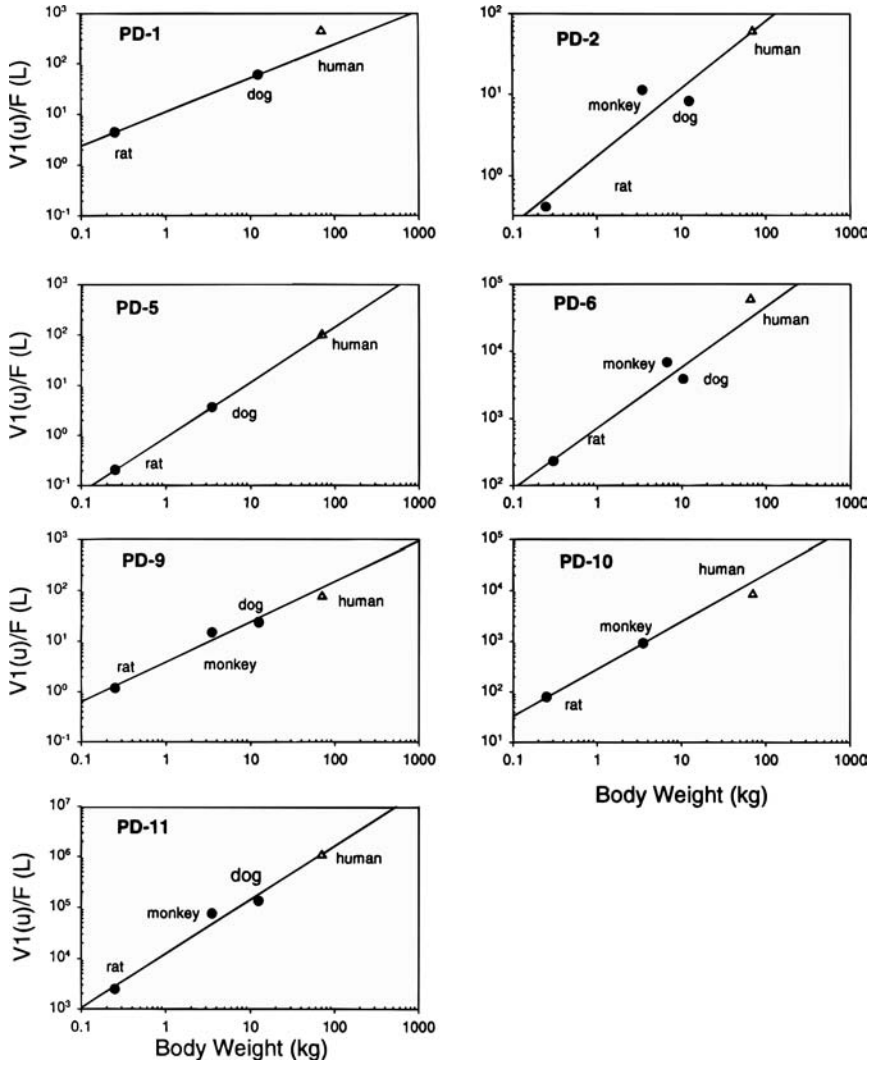

Fig. 5. Plots of the unbound $V1(u)/F$ versus body weight for orally dosed Parke-Davis compounds ($V1(u)/F = a \cdot W^b$).

Table 3. Estimated Human Oral Pharmacokinetic Parameters for Parke-Davis Compounds[c]

	Half-life (hr)		Cmax (μg/ml)		AUC (μg · hr/ml)		Bioavailability (%)		
							Actual		Predicted
	Actual	Predicted	Actual	Predicted	Actual	Predicted	Human	Animal (range)	Human
PD-1	5.0	4.1	0.87	2.05	6.72	12.7	81	63 (59–67)	97
PD-2	5.8	6.6	0.88	1.27	9.27	14.9	59	66 (40–80)	89
PD-5	5.3	7.5	1.54	1.09	11.2	12.5	90	77 (70–83)	100
PD-6	4.7	4.0	1.28	1.12	9.28	6.8	51	22 (12–39)	39
PD-9	1.1	2.4	2.23	1.25	6.56	5.06		42 (49–51)	39
PD-10	20.3	23.6	0.12	0.078	0.36	0.27		9.0 (6.0–12)	7.2
PD-11	5.5	5.4	1.23[a]	1.10[a]	10.4[b]	9.60[b]		6.1 (5.7–6.4)	3.5

[a] Cmax: ng/ml,
[b] AUC: ng · hr/ml., $AUC =$.
[c] Dose/(CL/F), $\%F = (CL) \cdot 100\%/(CL/F)$.

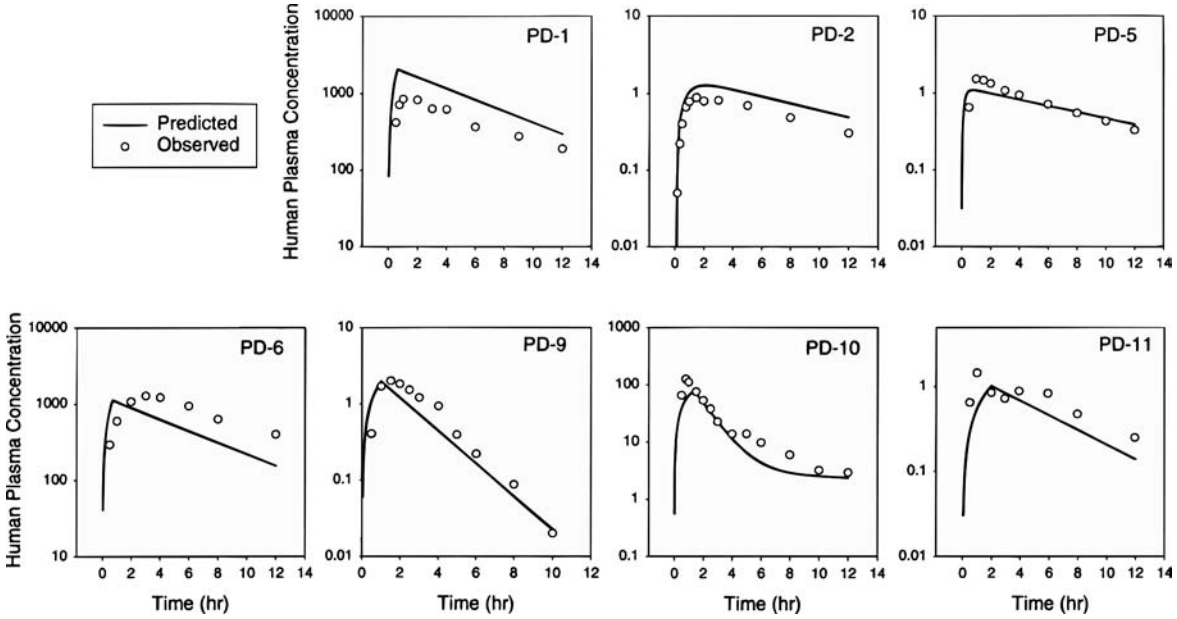

Fig. 6. Plots of the predicted versus the actual human plasma concentration-time profiles for 7 orally dosed Parke-Davis compounds.

(17,25,29–30). As mentioned in Dr. Obach's recent work, the effect of binding to microsomes and plasma proteins still needs to be considered when in vitro liver microsome approach is used.

CONCLUSIONS

In this work we proposed a simple allometric approach for predicting human system CL and oral CL/F and the results suggest that the correlation between the predicted and the actual values is greatly improved using unbound drug concentration and BRW correction. In addition to clearance, our data also suggest that human dose regimen and drug exposure (Cmax, AUC) could be reasonably predicted by a direct scale up of oral pharmacokinetic parameters. Assuming a 2-fold error is acceptable for early estimation in pharmaceutical companies, human parameters at estimated efficacious and toxic doses could be predicted prior to first trial in man. This would greatly help decision-making during new drug development.

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