Correlation of Plasma Clearance of 54 Extensively Metabolized Drugs Between Humans and Rats: Mean Allometric Coefficient of 0.66[1]

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Purpose. To evaluate the distribution of allometric exponents for relationship of total plasma clearance of 54 extensively metabolized drugs, with wide-ranging linear clearance values, between humans and rats, to provide a rationale for the observed data, and to discuss potential significance of the findings.

Methods. Human and rat plasma clearance values of 54 drugs with markedly different physicochemical properties were obtained from the literature. Standard allometric analysis was performed for each drug using both rat and human data. Unbound vs. total plasma clearances were obtained for 15 out of 54 drugs and their correlations between humans and rats were compared.

Results. The mean ± SD of the allometric exponent for the 54 drugs studied is 0.660 ± 0.190. The median clearance ratio based on unit body weight is 7.41 and the median exponent is 0.645. Excluding two outliers the correlation coefficient of plasma clearance between humans and rats was 0.745 ($p < 0.0001$). For the 15 drugs, use of unbound plasma clearance approach seems to significantly improve the correlation coefficient compared to total plasma clearance (0.940 vs. 0.841).

Conclusions. The present study indicates that on average, humans and rats may eliminate extensively metabolized drugs at a rate similar to that expected from the allometric or body surface area relationship of basal metabolic rate between the two species. A simple statistical distribution hypothesis is used to rationalize the species difference in plasma drug clearance. Rat may serve as an useful animal model to predict (unbound) plasma clearance of drugs in humans.

KEY WORDS: plasma clearance; unbound plasma clearance; interspecies scale-up in plasma clearance; allometric analysis; pharmacokinetics; rat vs. human.

INTRODUCTION

In recent years, there has been an increasing interest in the pharmacokinetic correlation among species or scale-up from animals to humans (1–17). It has been often reported that humans metabolize drugs much slower (four to seven times) than predicted from animals based on allometric analysis (1–2,5,7,9–11,16,17). The slower rate of metabolism in humans has been attributed to reasons such as enhanced longevity (2,5,9), larger brain size (2,11), diminished cytochrome P-450 mixed function oxidases with resulting less harmful byproducts (3,9), neoteny (18), or vertical allometry (3,5,18). In order to overcome this overprediction (intrinsic) plasma clearance per maximum lifespan potential (MLP) and/or brain weight have often been incorporated into allometric analysis (1,2,4,5,7,9–11,16,17). These approaches have been found to be successful in predicting human (intrinsic) plasma clearance of a number of drugs to date. An interesting phenomenon is that for some drugs plasma clearances in humans could be satisfactorily predicted based on the simple allometric method while for others incorporation of MLP or brain weight yielded unsatisfactory predictions in humans (11,16). The MLP or brain weight for humans is approximately four times longer or larger than predicted based on the allometric analysis of life expectancy in other mammals; the enhanced longevity or larger brain weight has been postulated to cause the slowdown of drug metabolism in humans (2,5,9,10).

Rat is probably the most widely used animal in preclinical pharmacokinetic studies. Reports on systematic comparison of plasma clearances between human and rat for a large number of extensively metabolized drugs appear to have been very limited to date. The purpose of this communication is to report our findings of the relationship of plasma clearances between humans and rats for 54 "randomly" selected, extensively metabolized drugs. The result obtained may be helpful to our using rat data to predict the first dose or therapeutic dose in humans during early clinical drug development (2,3,5,8,14,19,20). It may also be useful to test the general hypothesis of the MLP or brain weight theory between human and rat. In this regard, it is postulated that if the mean exponent from the simple allometric analysis of plasma clearances between human and rat for a large number of extensively metabolized drugs is similar to that (about 0.7) predicted based on the basal metabolic rate (3,5,14,21), then human and rat may be considered to have an overall similar elimination rate of extensively metabolized drugs (14,15). More correctly, unbound metabolic or unbound plasma clearance should probably be used as a gauge for metabolic/elimination rate comparison for extensively metabolized compounds (8,14,15).

METHODS

Plasma clearance data of 15 extensively metabolized drugs in both humans and rats reported from an earlier study (8) were first obtained. In view of availability of extensive human pharmacokinetic data compiled in an excellent reference (22), we first identified 205 out of 334 drugs that have their renal clearance less than 30% of total clearances. Among them 47 drugs were excluded from further consideration because clearance values were obtained from oral studies and there are uncertainties regarding the absolute bioavailability. A preliminary computer and library search for references containing reliable plasma clearance data in rats for most of the remaining 158 drugs were made and data on 39 drugs were obtained and used in the present analysis. Undoubtedly, more exhaustive literature search will yield clearance data on more drugs. It is, however, felt that the 54 drugs selected for analysis is quite adequate for the present study as they have very diverse physicochemical and pharmacological properties, and have very wide range of plasma clearance values. It is to be noted that plasma

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clearance data used were found or assumed to be in the linear range. Except for phenytoin whose plasma clearance in the linear range has been reported earlier (8), drugs such as salicylic acid and prednisolone known to show nonlinearity in elimination at therapeutic doses are not used. Drugs with only unbound human plasma or blood clearance reported in the table (22) were also excluded. Isoniazid was not used because of existence of fast and slow acetylators (22). For cyclosporine and tacrolimus, plasma clearances rather than reported (22) blood clearances were used in the present study.

The following allometric equation was used for the analysis:

$$CL = a\,(BW)^b \tag{1}$$

where CL is plasma clearance, "a" is the allometric coefficient and "b" is the allometric exponent. The "b" for each drug between rat and human was obtained by (14)

$$b = \frac{\log\left(\frac{CL_h}{CL_r}\right)}{\log\left(\frac{BW_h}{BW_r}\right)} \tag{2}$$

where the subscripts "h" and "r" refer to human and rat, respectively. A 70-kg body weight was assumed in all human studies while the weight for rat was based on the mean weight reported in each study or assumed to be 0.25 kg if not reported. The CL values used were assumed to be in the linear kinetic range in the present study. Also, a great majority (92%) of rat clearance values used here were obtained from male rats.

The unbound plasma clearance (CL_u) of drug was calculated by (14,15)

$$CL_u = \frac{CL}{f_u}$$

where f_u is the fraction of drug unbound in plasma.

RESULTS AND DISCUSSION

Human and rat clearance data, results of allometric analysis and clearance ratios between rat and human based on unit body weight are summarized in Table I. The mean ± SD of the allometric exponents for all the drugs was 0.660 ± 0.190. When two apparent outliers, diazepam and alprazolam were excluded, the mean exponent was increased slightly to 0.681 ± 0.162. The above mean data seem to indicate that overall, man and rat may metabolize or eliminate extensively metabolized drugs from the body at a rate similar to that expected from the body surface area or allometric analysis of basal metabolic rate (5,14,15,21). It has been stated that basal metabolic rate may reflect the overall reaction (metabolic) rate of all chemicals (probably in the hundreds or more) involved in the production of heat or energy from the entire body (14). In this regard, the liver also partly contributes to the overall basal metabolic rate. Our results also suggest that longevity, brain weight, specific enzyme activity, intelligence and neoteny may not play a significant role in the overall metabolism or elimination rate of drugs between human and rat. It is to be noted that quantitative or qualitative differences in the formation of metabolites between human and rat have been well documented. The insignificant role of neoteny in the slowdown of human metabolic rate of drugs has been pointed out (3).

The high variability in allometric exponent (0.12 for alprazolam to 1.06 for nifedipine with a median of 0.64 for 54 drugs) and in the rat/human plasma clearance ratio (0.7 for nifedipine to 123 for diazepam with a mean of 12.7 ± 22.3 or 8.61 ± 7.17 when two outliers were excluded; the median being 7.41 and 7.18 with and without the outliers, respectively) as shown in Table I seems interesting and probably somewhat unexpected. The mean rat/human plasma clearance ratio may be smaller if both male and female rats were equally used in the study. This is because male rats have sometimes been shown to metabolize drugs much faster than female rats (23).

When the exponent is greater than about 0.9 or the rat/human plasma clearance ratio is below 2, human may be perceived to have a faster rate of metabolism or elimination than rat compared to the mean ratio of drugs studied here or based on the conventional concept of much slower metabolic rates in humans. For nifedipine, human can actually eliminate this drug about 50% faster than rat. Interestingly, the phenomenon of "faster" elimination rates in humans does not appear to have been widely discussed in the literature. On the other hand, when the exponent is smaller than 0.5 or the rat/human clearance ratio is greater than 16, human may be perceived to eliminate drugs at a much slower rate than commonly anticipated. For oxazepam, phenylbutazone, valproic acid, alprazolam and diazepam, the plasma clearance per kg of body weight in rats are about 27, 32, 34, 116 and 123 times faster than in humans, respectively. Conventionally, these data may be rationalized by the vertical allometric concept or the longevity theory. However, one may also postulate that these slower metabolic or elimination rates in humans may be attributed to a simple statistical distribution phenomenon. In other words, based on unit body weight, man will be found to have a much slower metabolic rate than rat for some compounds, and to have a much faster rate than rat for other compounds. This is clearly shown in the distribution histogram (Fig. 1). In the present study 40 of the 54 drugs (74%) have a clearance ratio less than 12.

Based on the theory of "Hepatic Pharmacokinetic Stuff" per unit of body weight available in the MLP (2,10), one could estimate that the plasma clearance ratio per unit of body weight between rat and human (R) is approximately 20. This was based on the following relationship obtained from the MLP theory (2):

$$R = \frac{MLP_h}{MLP_r} \tag{3}$$

where MLP_h is 93.4 years and MLP_r is 4.68 years (2). This ratio is much greater than the median value of 7.18 found in the present study or the estimated 5 to 7 based on the basal metabolic rate relationship between human and rat (3,6,14,21). The above analysis indicates that the hepatic pharmacokinetic stuff theory can be used to explain the difference between human and rat when the R values are about 20. And it cannot be used to rationalize the difference when R values are either much smaller than 20 or much greater than 20.

There is generally a good correlation between human and rat plasma clearances for the 52 drugs (Fig. 2), which encompass a wide range of clearance values. Their correlation coefficient (r^2) is 0.745 with $p < 0.0001$. When all 54 drugs were analyzed, the r^2 is reduced to 0.662 with $p < 0.0001$. Although the correlation of CL between human and rat is highly significant,

Table I. Ratio of Rat to Human Total Plasma Clearances, and Allometric Exponents for 54 Drugs[a]

Drug	CL_h (ml/min/kg)	CL_r (ml/min/kg)	CL_r/CL_h	Exponent
Acetaminophen	5.00	43.1	8.6	0.618
Alprazolam	0.74	86.0	116.2	0.123
Amitryptiline	9.89	118.6	12.0	0.555
Amobarbital	0.56	10.3	18.6	0.482
Amphotericin B	0.46	1.93	4.2	0.746
Antipyrine	0.66	5.24	7.9	0.633
Azithromycin	9.0	34.0	3.78	0.764
Caffeine	1.40	12.5	9.0	0.611
Cefaperazone	1.20	23.88	19.9	0.469
Chorpromazine	4.29	60.6	14.1	0.530
Cyclosporine	7.80	6.11	0.78	1.05
Diazepam	0.35	43.2	123.4	0.138
Diclofenac	4.20	15.7	3.7	0.766
Diltiazem	12.0	86.2	7.3	0.648
Doxorubicin	17.0	44.26	2.6	0.822
Erythromycin	9.10	73.0	8.0	0.630
Ethinyl estradiol	5.40	64.0	11.9	0.561
Felodipine	12.0	84.75	7.06	0.657
Haloperidol	11.8	145.9	12.4	0.532
Hexobarbital	3.57	30.9	8.7	0.617
Imipramine	15.0	97.5	6.5	0.668
Isosorbide Dinitrate	45.0	118	2.6	0.829
Isosorbide-2-Mononitrate	5.80	19.3	3.3	0.916
Isosorbide-5-Mononitrate	1.80	5.00	2.8	0.819
ketoprofen	1.20	1.51	1.3	0.959
Lidocaine	9.20	23.6	2.6	0.833
Lorcainide	17.5	122	6.9	0.656
Meperidine	17.0	253	14.9	0.521
Metronidazole	1.30	5.18	3.98	0.755
Midazolam	6.60	67.0	10.2	0.589
Morphine	24.0	128	5.3	0.703
Nalbuphine	22.0	91.0	4.0	0.748
Nifedipine	7.00	4.88	0.7	1.064
Norethindrone	5.90	63.5	10.8	0.578
Omeprazole	7.50	61.8	8.2	0.635
Ondansetron	5.90	117	19.8	0.470
Oxazepam	1.05	28.0	26.7	0.417
Pentazocin	18.9	80.5	4.2	0.743
Pentobarbital	0.52	8.40	16.0	0.508
Pentoxifylline	60.0	77.8	1.3	0.954
Phenobarbital	0.06	0.75	12.8	0.548
Phenylbutazone	0.02	0.65	31.9	0.385
Phenytoin	0.57	7.40	12.9	0.546
Propranolol	15.0	92.0	6.1	0.678
Quinidine	4.49	33.8	7.5	0.642
Sumatriptan	16.0	38.0	2.4	0.846
Tacrolimus	8.10	26.7	3.3	0.772
Theophylline	0.86	2.69	3.1	0.856
Thiopental	3.90	5.30	1.4	0.946
Tolbutamide	0.18	1.37	7.6	0.640
Tolcapone	1.55	8.80	5.7	0.692
Valproic Acid	0.12	4.17	33.6	0.376
Verapamil	15.0	36.5	2.4	0.842
Warfarin	0.04	0.36	9.8	0.595
Average (54 drugs)			12.7	0.660
Standard Deviation			22.3	0.190
Average (52 drugs)[b]			8.6	0.681
Standard Deviation[b]			7.2	0.161

[a] References for rat CL are available upon request.
[b] Excluding diazepam and alprazolam.

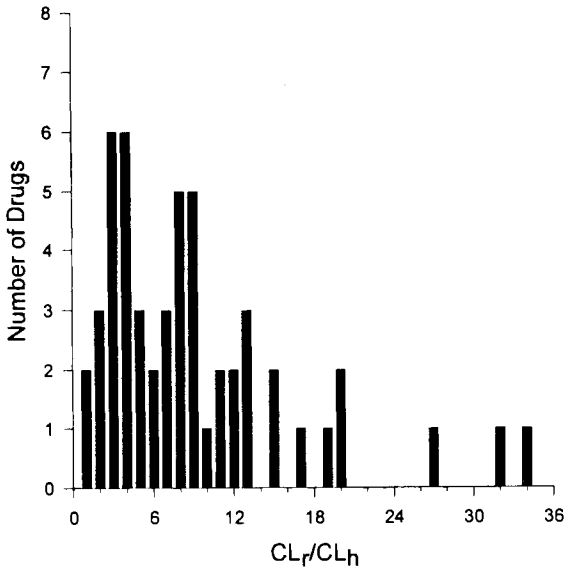

Fig. 1. Frequency distribution of total plasma clearance ratios between rat and human (CL_r/CL_h) for 52 drugs.

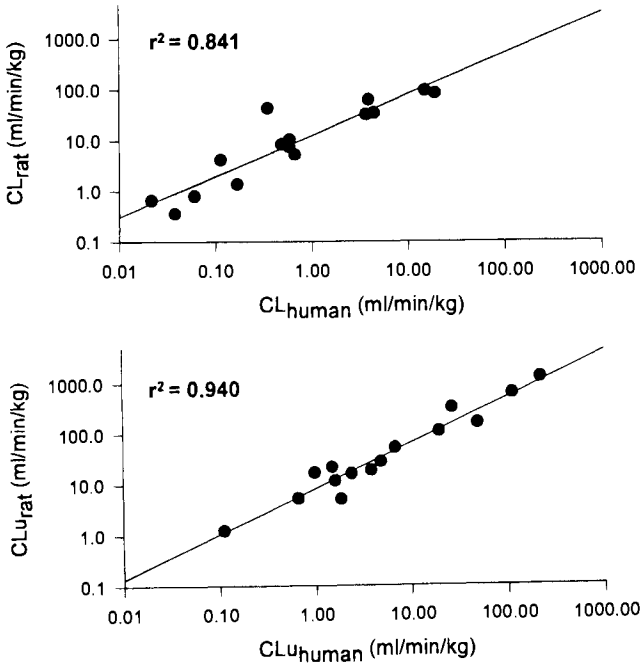

Fig. 3. Correlation of total plasma clearance (upper) and unbound clearance (lower) for 15 drugs between human and rat.

in view of wide variability for many drugs analyzed (Figs. 1 and 2), it appears that one should exercise caution in using rat CL to predict human CL in the first-time study in humans.

In an earlier study (14), use of unbound plasma clearance of 15 extensively metabolized drugs was found to improve their correlation between human and rat as compared to intrinsic unbound blood clearance. Since plasma protein binding data for most of other drugs are not readily available, only correlation of total plasma clearance and unbound plasma clearance of these 15 drugs between human and rat are compared here and their results are shown in Fig. 3. The correlation appears to be significantly improved by using the unbound clearance approach (r^2: 0.841 vs. 0.940). The mean exponent of the 15 drugs based on unbound clearance was 0.657 (14), that is practically identical to the mean of 0.660 found in the present analysis of total plasma clearance for the 54 drugs. The general magnitude of differences between rat and human appears to be significantly reduced when the unbound clearance approach is used, especially for drugs with extensive plasma protein binding. For example, for diazepam, phenylbutazone, valproic acid, phenytoin, warfarin and chlorpromazine, the ratios are reduced from 123 to 11.4, 31.9 to 6.8, 33.6 to 6.4, 12.9 to 5.7, 9.8 to 4.9, 14.1 to 4.7, respectively. For diazepam, the ratio will be further reduced to only 7.7 if a protein binding of 79.3% (24) rather than 84% (8) is used, and this ratio is much closer to that expected based on the basal metabolic rate concept (14). During the revision of this manuscript, we came across a recent reference (25) on tamsulosin, also an extensively metabolized drug. The extremely high clearance ratio of 213 between rat and human based on total plasma clearance would be reduced to only about 12 based on unbound plasma clearance. The above clearance and protein binding data are summarized in Table II.

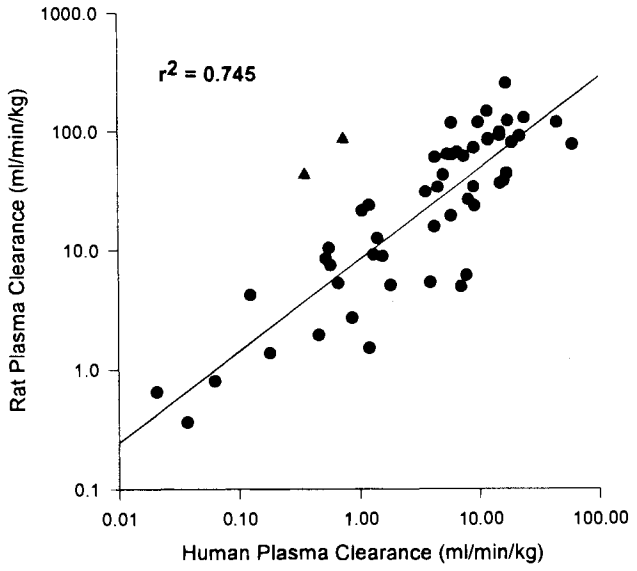

Fig. 2. Correlation of total plasma clearances of 52 drugs between human and rat (solid triangles: outliers not included in regression).

Table II. Comparison of Total and Unbound Plasma Clearance Ratios Between Rat and Human for Seven Drugs

Drug	% bound in plasma		CL_r/Cl_h Ratio	
	Rat	Human	Total drug	Unbound drug
Diazepam	86	98.7	123	11.4
Valproic acid	63.4	93	33.6	6.4
Phenylbutazone	95.8	99.1	31.9	6.8
Chlorpromazine	89.4	96.5	14.4	4.7
Phenytoin	72.3	88	12.9	5.7
Warfarin	98	99	9.8	4.9
Tamsulosin	80.6	98.9	213	11.9

Thus, potential marked differences in plasma protein binding between human and rat should be studied in early drug development. Differences in unbound fraction up to about 20 times could be found (Table II).

In an earlier study, diazepam was reported to show vertical allometry since prediction of its human plasma clearance based on data from rat, guinea pig, rabbit and dog was about 35 times higher (3); this is in sharp contrast with the above unbound plasma clearance analysis showing great similarity between human and rat. For antipyrine with negligible plasma protein binding, the human intrinsic clearance was reported to be 7-fold lower than predicted from 15 animal species (2). This is in contrast to the unbound or total plasma clearance ratio of 7.9 found in the present study indicating great similarity between human and rat. For phenytoin, the intrinsic clearance in humans was reported to be 4.4 times smaller compared to other four species including rat. In the present study, both human and rat appear to metabolize phenytoin at a similar rate based on unbound clearance. This also appears to be the case with caffeine that has a low plasma protein binding of about 15% (7). The rat/human plasma clearance ratio is only 8.96, in contrast to the report (7) that rat metabolizes caffeine 2–3 times faster than human. Similarly, man was reported to metabolize theophylline seven-fold slower compared to three other animal species including rat in an earlier study (26); in the present or early (15) study, however, man is shown to exhibit a metabolic rate similar to other species. Use of unbound clearance has also been shown to reduce the difference in metabolic rate of verapamil between human and rat (27).

The above analyses based on unbound clearance appear to provide a different perspective on the comparative rate of metabolism or elimination between different species. It is also expected that the wide scattering of the distribution histogram shown in Fig. 1 may be significantly reduced when unbound plasma clearances are used for comparison. The potential importance of unbound plasma clearance or unbound plasma concentration of drugs in the study of their pharmacodynamics and toxicity in humans and animals has been well recognized (28). This is because only the unbound drug, not the total drug, is generally regarded as the "driving force" for distribution to various tissues and receptor sites to elicit pharmacological or toxicological responses.

Although use of intrinsic hepatic clearance has been widely accepted in interspecies scaling or comparison, its potential limitations have been extensively discussed earlier (8,14). Compared to unbound CL, the intrinsic clearance does not directly predict the unbound plasma concentration or plasma area after dosing with known bioavailability except for drugs with low hepatic extraction ratio (6). Also, potential problems may arise if compounds are metabolized in other organs/tissues such as kidney, lungs, vascular beds and muscle (29).

The present study suggests that generally speaking, rat might serve as a good model to predict total or unbound plasma clearance of extensively metabolized drugs in humans. In view of the large variability in rat/human plasma clearance ratio, additional in vitro metabolic studies using hepatocytes or hepatic microsomes may be considered in scale-up (3–5,13,30). However, it seems that inaccurate prediction in CL may arise if the liver is not the major metabolic organ in humans or if a drug is mainly excreted unchanged in human but is mainly metabolized in the liver of rat. It is of interest to note that prediction of human plasma clearance of drugs based on a single species such as rat (4,8,14), dog (2,4), rabbit (4) and monkey (10) has been reported. Such an approach is encouraging in view of the good correlation between the maximum tolerated dose (based on body surface area) in patients and the LD_{10} (a dose producing 10% of fatality) in mice for a number of anticancer drugs (3,20). Moreover, the total plasma areas for each drug in patients and mice were generally similar (20) indicating similar (unbound) plasma clearances per unit of body surface area between the two species (14). Interestingly, success of animal scale-up to predict human pharmacokinetic parameters using several species has been regarded as scarce in view of a large number of drugs actually studied but not reported in the literature, apparently due to failure of satisfactory prediction (12). Weak allometric correlations of plasma clearance across veterinary and laboratory animal species for 44 drugs have been reported recently (17).

Satisfactory animal to human scale-up in plasma clearance has been most often reported for drugs that are mainly excreted intact in humans and animals (4–6). Whether or not the present findings could also be applied to drugs mainly excreted unchanged in the urine remains to be systematically studied. Limited data obtained from our laboratory to date and a preliminary review of literature seem to indicate a similar trend. The findings of the present and earlier (14,15) studies involving extensively metabolized drugs with vastly different plasma clearance values may thus seem especially interesting.

Accurate prediction of (unbound) plasma clearance in humans is important to the design of the first-time drug study in humans (3,6,14). Obviously, questions such as gastrointestinal absorption, first-pass gut, hepatic and pulmonary metabolism, apparent volume of distribution, terminal plasma half-life, active metabolite and linearity or nonlinearity of kinetic parameters may also need to be considered. In this regard, rat has been recently shown to serve as a good animal model to predict the fraction of oral dose absorbed in humans (31).

In summary, the present study of total plasma clearance of 54 extensively metabolized drugs and unbound plasma clearance of 16 extensively metabolized drugs between humans and rats indicates that overall, man and rat may metabolize or eliminate drugs or xenobiotics at a similar rate as expected from the relationship of basal metabolic rate between the two species. The much slower or much higher elimination rates of different compounds reported in humans compared to rats or perhaps also to other species of animals may be rationalized by a simple statistical distribution phenomenon. The present findings indicate that rat may generally serve as a good animal model to initially predict (unbound) plasma clearance in humans during early drug development. The study also shows the potential importance of using unbound plasma clearance for interspecies metabolic or elimination rate comparison.

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