Pharmaceutical Research, Vol. 5, No. 10, 1988

Report

Correlation of Unbound Plasma Clearances of Fifteen Extensively Metabolized Drugs Between Humans and Rats

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Received July 14, 1987; accepted April 21, 1988

Unbound plasma clearances (CLu) in humans and rats of 15 extensively metabolized drugs (phenytoin, hexobarbital, pentobarbital, phenylbutazone, warfarin, tolbutamide, valproate, phenobarbital, amobarbital, quinidine, chlorpromazine, propranolol, pentazocin, antipyrine, and diazepam), studied earlier by Sawada *et al.* (*J. Pharmacokin. Biopharm.* 13:477–491, 1985), were calculated. It was found that the ratio of CLu per square meter of body surface area between human and rat ranged from 0.38 for pentobarbital to 2.34 for tolbutamide, with a mean ratio of 1.07. When body weight (BW) was used for correlation, the mean CLu was proportional to $BW^{0.657 \pm 0.0935}$. A rationale for the above empirical findings is postulated. The present study seems to indicate the existence of a general similarity or predictability in the CLu of drugs between rats and humans. Low correlations were generally obtained when total (bound and unbound) plasma clearances were used for comparison.

KEY WORDS: animal scale-up in pharmacokinetics; unbound plasma clearance; plasma clearance; body surface area; basal metabolic rate; allometric equation.

INTRODUCTION

Recently, Sawada *et al.* (1) compared hepatic unbound intrinsic clearances (CLu_{int}, based on the well-stirred model and assumed to be in the linear range) of nine weakly acidic drugs (phenytoin, hexobarbital, pentobarbital, phenylbutazone, warfarin, tolbutamide, valproate, phenobarbital, and amobarbital) and six weakly basic drugs (quinidine, chlorpromazine, propranolol, pentazocin, antipyrine, and diazepam) in humans and rats. These 15 drugs are very extensively metabolized in the body (1). The mean ratio of their CLu_{int} per kilogram of body weight between rat and human is 13.1 and the individual ratio ranges from 2.69 for tolbutamide to 68.1 for diazepam, a 25.3-fold variation. The CLu_{int} has been regarded as the parameter that best gauges an organism's ability to fend off chemical assaults from ingested xenobiotics (2,3).

Since it is well known that the unbound drug concentration in plasma is most important in correlating with pharmacological effect and toxicity in the same or different species (1–8) and the body surface area (BSA) has been used to correlate with the plasma and renal clearance of total (bound and unbound) drug (9–11) and LD_{10} values of anticancer drugs (12) in different species, it would be of interest to investigate the relationship of unbound plasma clearances (CLu) of these 15 drugs in humans and rats in terms of unit BSA. It is important to note that in linear pharmacokinetics, the (mean) dosing rate divided by CLu will yield the (mean) steady-state unbound drug concentration in plasma, and the amount of drug absorbed to the general circulation after a single dose divided by the CLu will yield the total area under the unbound drug concentration from time zero to time infinity.

METHODS

The CLu for each drug was calculated by the following equation:

$$CLu = CL/fu \quad (1)$$

where CL is the plasma drug (bound and unbound) clearance and fu is the fraction of drug unbound in the plasma. The values used for CL (a summation of metabolic and renal clearances) and fu of 15 drugs were taken from the paper by Sawada *et al.* (1) except for warfarin (0.01 vs 0.08), valproate (0.07 vs 0.137), chlorpromazine (0.035 vs 0.430), and diazepam (0.013 vs 0.032), whose fu values (Table I) were based on those compiled by Benet and Sheiner (13). The use of these different fu values was initially prompted by our suspicion of the reported (1) unusually high values for warfarin (0.08) and chlorpromazine (0.43). Subsequently, the reported (1) fu values of all 15 drugs in humans were compared with those (when available) compiled more recently by Benet and Sheiner (13). When a major discrepancy between these two sources exists, the latter was adopted in the present study. It was found that the reported high fu values for warfarin and chlorpromazine were apparently due to printing errors because the reported (1) CLu_{int} values were calculated based on 0.008 and 0.043, respectively.

The BSA (in m^2) for rats in each study was estimated according to Meeh's formula (14).

$$BSA = K(BW)^{2/3} \quad (2)$$

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0724-8741/88/1000-0668$06.00/0

Table I. Correlation of CLu with BSA and BW in Humans and Rats for 15 Drugs

	CL (ml/min)	fu	CLu (ml/min)	BSA (m^2)	CLu/BSA (ml/min/m^2)	Ratio of CLu/BSA between human and rat	Mass exponent[a]
Phenytoin							
Human	40.8	0.12	340	1.73	197	1.13	0.685
Rat	2.22	0.277	8.01	0.046	174		
Hexobarbital							
Human	256	0.534	479	1.73	277	0.89	0.644
Rat	7.88	0.619	12.7	0.041	310		
Pentobarbital							
Human	33.8	0.49	69.0	1.73	39.9	0.38	0.497
Rat	2.31	0.504	4.59	0.044	104		
Phenylbutazone							
Human	1.52	0.009	169	1.73	97.7	0.96	0.658
Rat[b]	0.196	0.042	4.67	0.046	102		
Warfarin							
Human	2.68	0.01[c]	268	1.73	155	1.17	0.691
Rat	0.153	0.02	7.65	0.058	132		
Tolbutamide							
Human	11.7	0.09	130	1.73	75.1	2.34	0.829
Rat	0.370	0.268	1.38	0.043	32.1		
Valproate							
Human	7.94	0.07[c]	113	1.73	65.3	0.78	0.628
Rat	1.77	0.366	4.84	0.058	83.4		
Phenobarbital							
Human	4.25	0.543	7.83	1.73	4.53	0.59	0.574
Rat	0.200	0.639	0.313	0.041	7.63		
Amobarbital							
Human	41.1	0.39	105	1.73	60.7	0.46	0.523
Rat	2.58	0.481	5.36	0.041	131		
Quinidine							
Human	314	0.23	1370	1.73	790	1.25	0.704
Rat	8.45	0.325	26.0	0.041	634		
Chlorpromazine							
Human	275	0.035[c]	7860	1.73	4540	1.45	0.739
Rat	10.6	0.106	100	0.032	3130		
Propranolol							
Human	1050	0.068	15400	1.73	8930	1.22	0.698
Rat	25.3	0.0783	323	0.044	7340		
Pentazocin							
Human	1340	0.389	3430	1.73	1980	2.05	0.794
Rat	24.5	0.54	45.5	0.047	968		
Diazepam							
Human	24.5	0.013[c]	1890	1.73	1090	0.57	0.565
Rat	11.2	0.14	80.2	0.042	1910		
Antipyrine							
Human	46.3	1.00	46.3	1.73	26.8	0.76	0.621
Rat[b]	1.57	1.00	1.57	0.046	34.1		
Mean						1.07	0.657
SD						0.56	0.0935

[a] Calculated based on CLu values (in this table) and BW data reported in Ref. 1 according to Eq. (4).
[b] Body weight and body surface area were assumed to be 0.3 kg and 0.046 m^2, respectively.
[c] Based on data from Ref. 13.

where K is a constant (0.103 used in the present study) and BW is body weight in kilograms. The mean BSA for humans was assumed to be 1.73 m^2 in all studies.

RESULTS AND DISCUSSION

The results of analysis of 15 drugs are summarized in Table I and depicted in Fig. 1. There are two aspects that deserve special attention. First, variability in the ratio of CLu per square meter of BSA between human and rat is relatively low (coefficient of variation, 52.8%); the lowest ratio is 0.38 for pentobarbital, and the highest 2.34 for tolbutamide, the difference being only 6.2-fold. Second, the mean CLu/BSA ratio of the 15 drugs between human and rat is

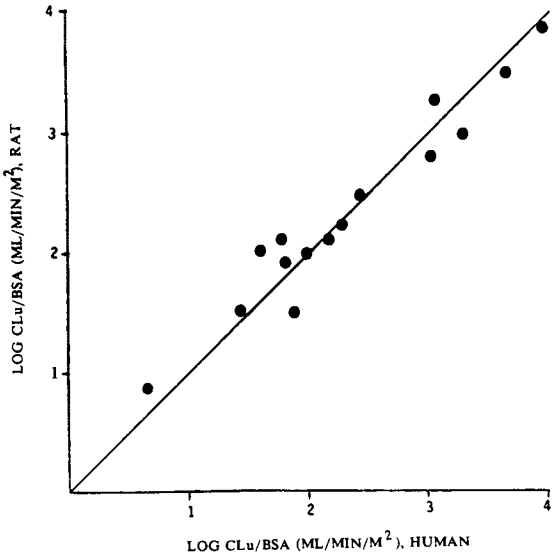

Fig. 1. Relationship of CLu//m² of 15 drugs in rat and human plotted on a log–log scale. The straight line has a slope of one.

1.07, which is hardly different from unity (Fig. 1). In view of numerous factors (such as dose dependency in elimination, environment, food, genetics, rhythm, sex, and age) that might affect drug elimination (1–3,5), the above results appear encouraging and indicate that the CLu/BSA method may serve as a potential useful alternative for interspecies extrapolation in drug elimination, especially between rat and human. In this regard, it seems noteworthy that the correlation coefficient between log CLu and log BSA for chlorothiazide in human, monkey, and rat is 0.9995, and those for six β-lactam antibiotics (ceftetan, cefmetazole, cefoperazone, moxalactam, cefpiramide, and cefazolin) in six species (mouse, rat, rabbit, dog, monkey, and human) are 0.989, 0.968, 0.981, 0.982, 0.982, and 0.973, respectively (15). These seven drugs are mainly excreted unchanged in urine and their tubular secretion is generally very extensive.

Although interspecies correlations of CL, renal clearance, and toxicity of many compounds have previously employed the BSA concept (9–12), we are not aware of any studies that show a correlation between CLu and BSA (also true for correlation with body weight), especially for compounds that are very extensively metabolized in the body. Since the toxicity may be more closely related to the unbound plasma concentrations or total area under the unbound plasma concentration–time curve after a single dose, the reported similar LD_{10} values per square meter of BSA for many anticancer agents (12) in different species are therefore also consistent with the prediction from the present CLu/BSA approach. The above discussions are somewhat different from an early report (2) showing considerable error in the interspecies (between dog and human) extrapolation of pharmacokinetics of benzodiazepines.

In recent years, the allometric approach has been extensively used to study interspecies (usually involving more than two species) differences in physiology, biochemistry, and pharmacokinetics (7,16,17). This approach [Eq (3)] was therefore chosen for comparison.

$$CLu = a\,(BW)^b \tag{3}$$

where a and b are the coefficient and exponent of the allometric equation. The b for each drug between rat and human was obtained by

$$b = \frac{\log(CLu_h/CLu_r)}{\log(BW_h/BW_r)} \tag{4}$$

where the subscripts h and r refer to human and rat, respectively. The results of analysis are also summarized in Table I. The mean ± SD of b for the 15 drugs studied is 0.657 ± 0.0935.

The attainment of the above mean b value is not surprising since the BSA is known to be proportional to $BW^{2/3}$ and the K values [Eq. (2)] used for the rat and human (based on 1.73 m² for 70 kg BW) are virtually identical (0.103 vs 0.102). The K values may, however, differ up to about *three times* among some mammals (14,18). Therefore, in some interspecies correlations a compared parameter may be proportional to BSA but not to $BW^{2/3}$ (19).

The rationale for the above *empirical* relationships appears intriguing; it is probably difficult to propose a scientifically rigorous reason to account for the findings. It is, however, of interest to note that the basal metabolic rates (BMR) per square meter of BSA between rat and human are virtually identical [850 vs 833 cal/m² (14)]. Since the unbound form in plasma is usually the driving force for distribution into cells where metabolism takes place, the BMR should probably reflect the mean CLu for all "natural" body substances involved in basal metabolism. It is possible that the body's ability to metabolize and excrete all xenobiotics, as reflected by their mean CLu, may also be proportional to its BMR. In other words, the *mean* Clu for *all* xenobiotics in rat and human probably should be approximately proportional to their BSA or $BW^{2/3}$. Obviously, more studies are needed in order to substantiate the above hypothesis. It is to be noted that when the reported relationship between BW and BMR in human and rat (14) was evaluated, the BMR was found to be proportional to $BW^{0.707}$, slightly different from the $BW^{2/3}$ relationship discussed above.

The reported mammalian interspecies relationship between BW and BMR should be mentioned here. It appears that the 0.75 power rule of Kleiber (20) has been most widely used in recent years (3,7,21–23). However, the validity of this rule has been questioned (19,25,26). For example, when more species (42 vs 12) covering a wider range of body weight (2.5 to 3.8 × 10^6 g) were considered (24), the mass exponent (b) was reduced from 0.75 to 0.66 (the 0.75 value was still recommended for mammals with a BW of 200 g and higher). The mass exponent was decreased to 0.43 (24) or 0.61 (17) when animals weighing 2.5–100 or 8–270 g were compared. A reanalysis of the data of Kleiber also revealed (25) the likelihood of a systematic bias in the earlier analysis because of the neglect of circadian rhythms, and correction for this bias should produce a mass exponent closer to 0.67. It is important to note, however, that when the intraspecies relationship between BW and BMR was evaluated, the mass exponents in most species were found to be about 0.67 (18,19). It is also of interest that six world weight-lifting records were correlated with $BW^{0.67}$ (21).

The correlation between human and rat became less obvious and more erratic for the present 15 drugs when com-

parison was made based on CL per unit of BSA; the mean ± SD ratio between human and rat was 0.596 ± 0.374, and the individual ratio ranged from 0.0529 for diazepam to 1.06 for propranolol, a 20-fold variation. Their individual values according to the order of drugs listed in Table I are 0.489, 0.768, 0.369, 0.206, 0.585, 0.786, 0.149, 0.501, 0.373, 0.885, 0.479, 1.06, 1.48. 0.0529, and 0.76. This was also true when the allometric approach was employed, the mean b ± SD being 0.526 ± 0.155. Similar phenomena were also found for some of the six β-lactam antibiotics studied (15).

The BSA concept has been successfully employed to scale oral absorption of chlorothiazide in rat and man (26,27). When oral doses were calculated based on unit BSA, marked dose-dependent bioavailability (ranging from 9 to 57%) profiles from these two species became virtually superimposable, while considerably different profiles would result if the doses were based on unit body weight. This finding has been attributed to similarity in gross surface area of the small intestine (perhaps also the large intestine) in terms of 1 m^2 of BSA in both species and, also, to their similarity in intestinal transit time (26,27).

The CLu_{int} concept has been valuable in studying interspecies difference or similarity in hepatic elimination (1–3,7,8, and references therein). Proper use of the approach may require an accurate assessment of *in vivo* CLu_{int}. To accomplish this, one may need to have a proper hepatic modeling (28,29) (potential marked overestimation of "real" *in vivo* CLu_{int} by the well-stirred model for high-clearance drugs has been reported in Ref. 28), a quantitative understanding of the contribution of nonhepatic metabolism to total metabolic clearance (30), an accurate measurement of hepatic blood flow (1) (e.g., the value of CLu_{int} may change two to four times due to a 30% change in flow rate), a clear understanding of the role of protein binding in hepatic clearance (8,31, and references therein), and an accurate assessment of the plasma/blood concentration ratio (8,32,33). Estimates of CLu_{int} may also be complicated by the fact that a drug in erthrocytes, in either free or bound form, may behave quite differently from that in plasma during its passage through the liver due to the relative slowness in transmembrane transport of drugs (34); this is quite different from that assumed in most conventional hepatic models (29). In contrast, the present CLu approach based on either BSA or BW (the mass exponent may generally range between about 0.65 and 0.75) appears relatively simple in concept, calculation, and application and may serve as a useful guide for dosing in the early evaluation of efficacy and/or toxicity of xenobiotics.

It seems of interest to note that in an early study (35), the CLu_{int} of antipyrine, one of the drugs evaluated in this paper, was successfully scaled to $BW^{0.865}$ in 10 animal species, and its CLu_{int} in humans was only sevenfold lower than predicted based on the allometric relationship obtained from the animals. This appears to be in sharp contrast with the present study, showing a great similarity in CLu based on unit BSA (Table I). The reason for the apparent discrepancy between the present and the previous (35) studies remains to be explored. Perhaps, one may postulate that both man and rat are slower metabolizers of antipyrine compared to most other animal species.

Finally, it seems worthwhile to point out that in using the conventional physiological approach for interspecies scaling in plasma drug concentration vs time profiles (7,36), one should be aware of implications of having marked sampling site-dependent drug concentrations in the blood (36–38). For example, the disposition functions of a drug after intravenous administration to a subject may vary greatly and resemble those from two different drugs, depending upon whether arterial or venous blood is used for analysis.

ACKNOWLEDGMENTS

This research was supported in part by a fund from the University of Illinois Foundation. F.H.H. is a 1983–1986 Squibb–AFPE Biopharmaceutics/Pharmacokinetics Fellow. The authors wish to thank Dr. Joyce Mordenti for her valuable critiques of the manuscript.

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