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Prediction of the Disposition of Nine Weakly Acidic and Six Weakly Basic Drugs in Humans from Pharmacokinetic Parameters in Rats

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Various pharmacokinetic parameters—disposition half-life, $t_{1/2,z}$, metabolic clearance CL_m, volume of distribution V, intrinsic clearance of unbound drug CLu_{int}, and unbound volume of distribution of tissues (distributive tissue volume/fraction of drug in tissue unbound, V_T/fu_T—are compared in rat and human for 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. With regard to all parameters, statistically significant correlations are obtained when parameters are plotted on a log-log plot. Correlation coefficients between the intrinsic parameters (CLu_{int} or V_T/fu_T) were higher than those between the hybrid parameters ($t_{1/2,z}$, CL_m or V). In general, these drugs were metabolized ten times more rapidly in rat than in human. With regard to the tissue distribution of these drugs, there was little difference between rat and human. Predictions of CL_m, V, and $t_{1/2}$, in humans using rat data were successful for most drugs, with a few marked exceptions.

KEY WORDS: animal scaleup; rat; human; weakly acidic drug; weakly basic drug.

INTRODUCTION

There have been a number of reports dealing with interspecies variation in drug metabolism and renal clearance (1-7). Pharmacokinetic principles were applied by Boxenbaum (8-10) and Sawada *et al.* (11) in the extrapolation of animal data to humans. Boxenbaum compared the metabolic intrinsic clearances CLu_{int} of antipyrine, phenytoin, and benzodiazepines in humans with those in animals and found that CLu_{int} in the human was approximately one-seventh of what would be predicted from other species (8). Furthermore, he demonstrated an allometric relationship between CLu_{int} of antipyrine (AP), phenytoin (DPH), and clonazepam per maximum life-span potential

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and body weight, and suggested that the lesser quantitative ability of humans to metabolize many drugs may be correlated with their enhanced longevity (9). Recently, Boxenbaum compared the pharmacokinetic parameters for 12 benzodiazepines in dog and human, and simultaneously made extrapolations from dog to human (10). Sawada *et al.* (11) compared the pharmacokinetic parameters half-life $t_{1/2}$, total body clearance CL_p, renal clearance CL_R, hepatic clearance CL_H, volume of distribution V, intrinsic clearance of unbound drug CLu_{int}, and unbound volume of distribution of tissues (distributive tissue volume/fraction of drug in tissue unbound, V_T/fu_T) for six β-lactam antibiotics in mouse, rat, rabbit, dog, monkey, and human, and two methods for extrapolation of the disposition of β-lactam antibiotics from animals to humans were presented. One was the Adolph-Dedrick approach, which can be used to predict clearances in human from the relationship between CL_{int} of unbound drug and body weight in several animal species (11). The other was the Boxenbaum approach, which predicts pharmacokinetic parameters of β-lactam antibiotics using the regression line of a log-log plot of CLu_{int} and V_T/fu_T between one species (monkey) and human (11). To date studies have been restricted to the benzodiazepines, DPH, AP, and β-lactam antibiotics.

In the present study, the literature was searched for pharmacokinetic data on nine weakly acidic drugs, phenytoin (DPH), hexobarbital (HXB), pentobarbital (PEB), phenylbutazone (PBZ), warfarin (WA), tolbutamide (TB), valproate (VA), phenobarbital (PB), and amobarbital (AB), and six weakly basic drugs, quinidine (QD), chlorpromazine (CPZ), propranolol (PL), pentazocine (PZ), diazepam (DZP), and antipyrine (AP). The Boxenbaum approach to the prediction of the pharmacokinetic parameters $t_{1/2,z}$, V, and CL_m of various drugs using the regression line of a log-log plot of CLu_{int} and of V of unbound drug between rat and human was investigated.

METHODOLOGY

Boxenbaum Approach

The following journals were mainly searched for kinetic data of various drugs: *J. Pharmacokin. Biopharm.*, *J. Pharm. Sci.*, *J. Pharmacol. Exp. Ther.*, *J. Pharm. Pharmacol.*, *Clin. Pharmacol. Ther.*, *Eur. J. Clin. Pharmacol.*, *Br. J. Clin. Pharmacol.*, and *Br. J. Pharmacol.* Papers were chosen in which the time course of plasma or serum concentrations after intravenous administration of various drugs was measured in rat or human; the values of V and CL were taken as those calculated by the original authors. In the case of WA and PBZ, oral data in the human were utilized, since these drugs are

completely absorbed after oral administration and the first-pass effect is negligible (12). Furthermore, papers were sought giving values of the plasma unbound fraction *fu* and the blood-to-plasma concentration ratios C_b/C in rat and human. In the case of nonlinear binding to plasma proteins and blood cells (QD and TB in rats), the binding parameters *fu* and C_b/C were calculated over the range of concentrations found in the *in vivo* studies. Namely,

$$fu = \bar{C}u/\bar{C} \tag{1}$$

$$C_b/C = \bar{C}_b/\bar{C} \tag{2}$$

where $\bar{C}u$, $\bar{C}$, and $\bar{C}_b$ are the mean plasma unbound concentration, the total concentration, and the blood concentration, respectively, which were calculated mathematically by the equations

$$\bar{C}u = AUCu_{0\to t}/t \tag{3}$$

$$\bar{C} = AUC_{p,0\to t}/t \tag{4}$$

$$\bar{C}_b = AUC_{b,0\to t}/t \tag{5}$$

where t is the last sampling time after administration of the drugs.

With the exception of QD and PB in both rat and human, less than 3% of the dose of the drugs could be recovered unchanged in urine. Available data in rat indicate that except for PEB (17), metabolites rather than drug are excreted in bile (13-16). Therefore, the plasma clearance CL_p was taken to be equal to the sum of metabolic clearance CL_m and renal clearance CL_R. Since CL_m did not exceed the value of hepatic blood flow Q_H, the liver was assumed to be the sole metabolizing organ. The following equations were utilized to calculate the intrinsic clearance CLu_{int}:

$$CL_p = CL_R + CL_m = \frac{D_{iv}}{AUC_{iv,p}} \tag{6}$$

$$CL_m = CL_p - CL_R \tag{7}$$

$$CL_m = \frac{Q_H \cdot fu \cdot CLu_{\text{int}} \cdot (C_b/C)}{(C_b/C) \cdot Q_H + fu \cdot CLu_{\text{int}}} \tag{8}$$

$$CLu_{\text{int}} = \frac{1}{fu} \cdot \frac{(C_b/C)(CL_p - CL_R)Q_H}{(C_b/C)Q_H - (CL_p - CL_R)} \tag{9}$$

The following assumptions were made in Eq. (8) (18):

1. Intimate mixing takes place between the hepatic portal blood and the hepatic arterial blood before drug partitions into the sinusoids.
2. Only unbound drug can traverse membranes.
3. There is no diffusional barrier between the drug in blood and the enzyme within the hepatocytes; that is, the rate of distribution is perfusion-limited.

Table I. Pharmacokinetic Parameters of Nine

Drug	Species	$t_{1/2,z}$ (min)	CL_m (ml/min per kg)	CL_R (ml/min per kg)	V_{ss} (L/kg)	V (L/kg)	*fu*	C_b/C
Phenytoin	Human	792	0.574	0.00	—[a]	0.640	0.120[b,c,d]	0.610[e]
(DPH)	Rat	162	7.40	0.00	—[a]	1.39	0.277[b,c,f]	0.990[e]
Hexobarbital	Human	261	3.57	0.00	1.10	1.27	0.534[c,g]	1.00[h]
(HXB)	Rat	19.1	30.9	0.00	0.701	0.850	0.619[b,c,f]	1.00[e]
Pentobarbital	Human	1340	0.524	0.00	0.990	0.999	0.490[b,c,i]	0.95[j]
(PEB)	Rat	144	8.37	0.0340	1.64	1.75	0.504[b,c,f]	1.56[e]
Phenylbutazone (PBZ)	Human	4110	0.0205[k]	0.00	0.122[k]	—[a]	0.0090[g,l]	0.58[m]
	Rat	126	0.654	0.00	0.236	—[a]	0.0420[c,g]	0.58[m]
Warfarin	Human	2040	0.0367	0.00	—[a]	0.108	0.080[b,c,f]	0.58[m]
(WA)	Rat	424	0.360	0.00	—[a]	0.220	0.0200[b,c,f]	0.58[m]
Tolbutamide	Human	434	0.180	0.00	—[a]	0.112	0.0930[c,g]	0.752[h]
(TB)	Rat	110	1.37	0.00	—[a]	0.216	0.268[c,g]	0.752[e]
Valproate	Human	732	0.124	0.00	0.131	0.137	0.113[b,f]	0.280[n]
(VA)	Rat	276	4.17	0.00	0.657	1.66	0.366[b,f]	0.740[n]
Phenobarbital	Human	5940	0.0486	0.0139	0.542	—[a]	0.543[b,o,p]	0.861[j]
(PB)	Rat	903	0.750	0.0500	1.02	1.04	0.639[b,c,f]	1.59[e]
Amobarbital	Human	1360	0.556	0.00	1.01	1.04	0.390[c,g]	1.48[h]
(AMB)	Rat	103	10.3	0.0210	1.46	1.54	0.481[b,c,f]	1.48[e]

[a] A dash indicates not determined or no information.
[b] Determined by the equilibrium dailysis method.
[c] Determined at 37°C.
[d] Determined at *p*H 7.38.
[e] Determined by the *in vitro* centrifugation method.
[f] Determined at *p*H 7.40.
[g] Determined by the ultrafiltration method.
[h] Assumed to be equal to the same value of rat.
[i] Determined at *p*H 7.35.

4. The rate of drug elimination is a function of the contraction of unbound drug bathing the enzymes.
5. The liver is a single, well-stirred compartment.
6. Distribution equilibrium is achieved so rapidly that drug in the emergent venous blood is in equilibrium with that in the liver. Assuming passive diffusion, it then follows that the concentrations of unbound drug in the venous blood and in the liver are equal.
7. Linear conditions hold for *fu*, C_b/C, and CLu_{int}.

The total amount of drug in all tissue compartments divided by the concentration of unbound drug in plasma is given by the following equation

Weakly Acidic Drugs in Rat and Human[a]

CLu_{int} (nl/min per kg)	$(V_V/fu_T)_{ss}$ (L/kg)	V_T/fu_T (L/kg)	Number of subjects	Sex	Body weight (kg)	Dose (mg/kg)	Route of adminis-tration	Ref.
4.85	—[a]	4.93	4	M	71.0	2.00	i.v.	38, 39
37.8	—[a]	4.71	4	M	0.300	10.0	i.v.	33, 36
7.78	1.91	2.23	4	M	71.6	7.37	i.v.	40, 41
90.5	1.00	1.24	—[a]	M	0.255	60.0	i.v.	37, 42
1.09	1.87	1.88	7	M, F	64.5	100	i.v.	43, 44
18.0	3.01	3.22	—[a]	M	0.275	40.0	i.v.	45
2.28	8.36	—[a]	—[a]	—[a]	—[a]	—[a]	—[a]	46
			1M, 4F	M, F	67.5	2.96	p.o.	67
			5M, 1F	M, F	—[a]	6.00	p.o.	68
			3	F	69.0	8.70	p.o.	69
			6	—[a]	84.0	5.00	p.o.	70
15.8	4.49	—[a]	—[a]	M	—[a]	12.5	i.v.	14
4.59	—[a]	7.70	10	M	73.0	0.685	p.o.	47
18.2	—[a]	8.68	13	M	0.425	0.600	i.v.	29
1.96	—[a]	0.558	3	M	65.0	15.4	i.v.	48
5.27	—[a]	0.582	3	M	0.270	80.0	i.v.	49
1.12	0.961	1.01	6	—[a]	64.0	6.25	i.v.	50
12.4	1.63	4.37	—[a]	M	0.425	200	i.v.	51
0.0896	0.871	—[a]	4(M), 2(F)	M, F	68.0	1.91	i.v.	52–54
1.18	1.40	1.43	—[a]	M	0.250	10.0	i.v.	45
1.45	2.28	2.37	7	M	74.0	3.54	i.v.	55, 56
23.8	2.79	2.95	—[a]	M	0.250	10.0	i.v.	45

[j]Determined by the *in vitro* equilibrium dialysis method.
[k]Calculated from the plasma concentration-time curves using SALS program (66).
[l]Determined at 25°C.
[m]Since the value of *fu* is small, C_b/C was estimated as $(1 - H_t)$ using the value of 0.42 for H_t.
[n]The *in vivo* C_b/C ratio after intravenous administration of drugs, determined by the centrifugation method.
[o]Determined at 8°C.
[p]Determined at *p*H 7.20.

(19, 20):

$$\frac{V_T}{fu_T} = \frac{V_{ss} - V_b C_b/C}{fu} \tag{10}$$

where V_B and V_{ss} are the blood volume and the volume of distribution at steady state, respectively. The terminal half-life $t_{1/2,z}$ is given by

$$t_{1/2,z} = \frac{\ln 2}{\lambda_z} = \frac{\ln 2 \cdot V}{CL_p} \tag{11}$$

where λ_z is the elimination rate constant at the terminal phase. Reported or calculated values for the parameters CL_m, V, and $t_{1/2,z}$ were averaged

Table II. Pharmacokinetic Parameters of Six

Drug	Species	$t_{1/2,z}$ (min)	CL_m (ml/min per kg)	CL_R (ml/min per kg)	V_{ss} (L/kg)	V (L/kg)	fu	C_b/C
Quinidine	Human	470	2.91	1.58	—[a]	3.02	0.230[b,c,d]	0.920[e]
(QD)	Rat	55.4	33.8	0.00	—[a]	6.00	0.325[b,c,d]	1.40[e]
Chlorpro-								
mazine	Human	1810	4.29	0.00	11.2	—[a]	0.430[b,d,f]	1.56[g]
(CPZ)	Rat	333	60.6	0.00	29.1	—[a]	0.106[b,d,f]	1.56[h]
Propranolol	Human	167	11.2	3.80[i]	—[a]	3.62	0.0680[b,d,f]	0.810[j]
(PL)	Rat	39.9	26.1	65.9[i]	—[a]	5.30	0.0783[b,d,f]	0.800[j]
Pentazocin	Human	203	18.3	0.639	4.58	5.56	0.389[b,c,l]	1.06[h]
(PTZ)	Rat	126	78.2	2.27	7.66[m]	11.6[m]	0.540[b,c,d]	1.55[e,j]
Diazepam	Human	1970	0.35	0.00	0.890	0.950	0.032[b,d,f]	1.04[g]
(DZP)	Rat	66.6	43.2	0.00	5.30	7.26	0.140[b,c,d]	1.04[e]
Antipyrine	Human	654	0.662	0.00	—[a]	0.869	1.00	1.00
(AP)	Rat	122	5.24	0.00	—[a]	0.602	1.00	1.00

[a] A dash indicates not determined or no information.
[b] Determined by the equilibrium dialysis method.
[c] Determined at 37°C.
[d] Determined at *p*H 7.40.
[e] Determined by the *in vitro* centrifugation method.
[f] Determined at 25°C.
[g] Assumed to be equal to the value for the rat.

from the data on individual subjects. The values of CLu_{int} were calculated from the average values of CL_m and fu, and the values of V_T/fu_T were calculated from the average values of C_b/C and fu. The value of Q_H was taken as 69.1 and 25.4 ml/min per kg body weight for rat and human, respectively (8). The value of V_B was taken as 0.08 L/kg in both rat and human (21). All data were plotted on a log-log scale and the linear regression of the logarithmic values was calculated by the least-squares method to give the parameters in the power law formula

$$y = Ax^B \tag{12}$$

where y is the ordinate and x is the abscissa.

RESULTS AND DISCUSSION

Boxenbaum Approach for Studying Interspecies Variation

Boxenbaum (10) compared the pharmacokinetic parameters for 12 benzodiazepines in dog and human, and simultaneously predicted the values of CL_p, V, and $t_{1/2,z}$ in the human. In the present study, we make extrapolations from one species (rat) to the human for the pharmacokinetic parameters of nine weakly acidic drugs and six weakly basic drugs. Tables I

Weakly Basic Drugs in Rat and Human[a]

CLu_{int} (ml/min per kg)	$(V_T/fu_T)_{ss}$ (L/kg)	V_T/fu_T (L/kg)	Number of subjects	Sex	Body weight (kg)	Dose (mg/kg)	Route of administration	Ref.
24.2	—[a]	12.8	4(M), 1(F)	M, F	—[a]	4.00-5.0	i.v.	57, 58
160	—[a]	18.1	5	M	0.250	30.0	i.v.	135
112	258	—[a]	13	—[a]	64.0	0.391	i.v.	59, 60
1310	273	—[a]	10	M	0.175	10.0	i.v.	59
1650	—[a]	52.3	9	M	—[a]	20.0[k]	i.v.	31
11100	—[a]	66.9	5	M	0.275	2.50	i.v.	31
131	11.6	14.1	5	M	70.5	0.519	i.v.	61-64
537	14.0	21.2	—[a]	M	0.305	0.500	i.v.	17
11.1	25.2	27.1	10	M	—[a]	0.100	i.v.	4, 34
756	37.3	51.3	5	M	0.260	1.20	i.v.	22, 65
0.679	—[a]	0.522	—[a]	—[a]	—[a]	—[a]	i.v.	8
5.68	—[a]	0.789	—[a]	—[a]	—[a]	—[a]	i.v.	8

[h]Determined by the *in vitro* equilibrium dialysis method.
[i]Extrahepatic clearance (31).
[j]The *in vivo* C_b/C ratio after intravenous administration of drugs, determined by the centrifugation method.
[k]Dose per head.
[l]Determined at *p*H 7.35.
[m]Calculated from the plasma concentration-time curves using the SALS program (66).

and II show all data used in the present study. The hybrid parameters $t_{1/2,z}$, CL_m and V in rat and human were plotted against each other on a log-log scale. Figures 1 and 2 show these plots for $t_{1/2,z}$, CL_m, and V (or V_{ss}). Using the regression equation (Fig. 1), one finds that a drug with $t_{1/2,z} = 1.00$ hr in the rat would have $t_{1/2,z} = 8.55$ hr in the human. These findings are similar to the relationship between dog and human for $t_{1/2,z}$ of benzodiazepines (10).

As shown in Fig. 2 (left), the rat clears the total drug in the blood 9-14 times more rapidly than does the human. With respect to $t_{1/2,z}$ and CL_m, statistically significant correlations were observed for these parameters between rat and human ($p < 0.01$ and $p < 0.001$, respectively). With regard to V (right of Fig. 2), the observed values for VA and DZP showed a discrepancy from the regression line, although the correlation was statistically significant ($p < 0.01$). The V and CL_m of four basic drugs (QD, PL, CPZ, and PEB) in both rat and human tend to be greater than those of the acidic drugs. As shown in Fig. 3, correlation coefficients between the intrinsic parameters CLu_{int} or V_R/fu_T were higher than those between the hybrid parameters CL_m, V, and $t_{1/2,z}$, while the CLu_{int} of DPZ and the V_T/fu_T of VA showed a discrepancy from the regression line. Variations due to Q_H and/or fu may have been eliminated from the CL_m and V. The values of the coefficient of determination r^2 for the hybridized parameters in Fig. 2

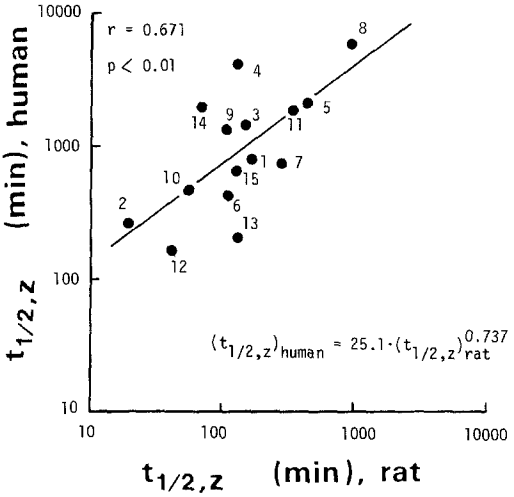

Fig. 1. Correlation between the half-life of the terminal exponential phase of various drugs in rat and human. (1) DPH, (2) HEB, (3) PEB, (4) PBZ, (5) WA, (6) TB, (7) VA, (8) PB, (9) AMB, (10) QD, (11) CPZ, (12) PL, (13) PTZ, (14) DZP, and (15) AP.

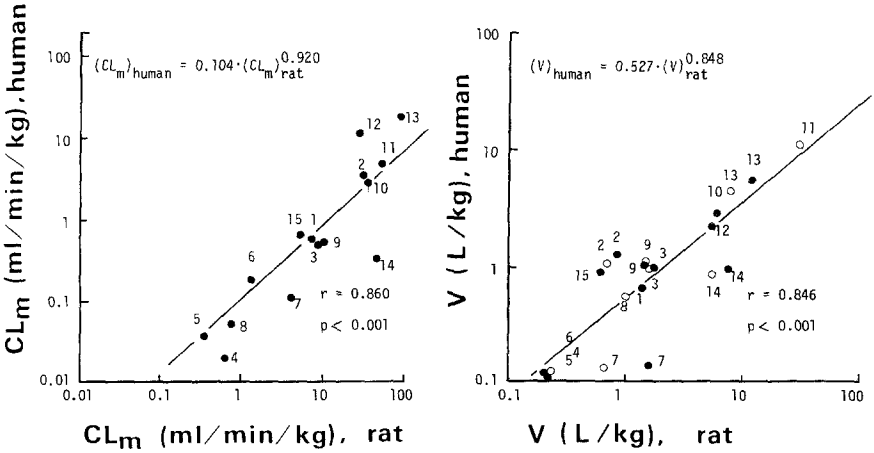

Fig. 2. Correlation between the hybridized parameters of various drugs in rat and human. Left: metabolic plasma clearance; right: volume of distribution (●) V and (○) V_{ss}. The numbering of the drugs is as in Fig. 1.

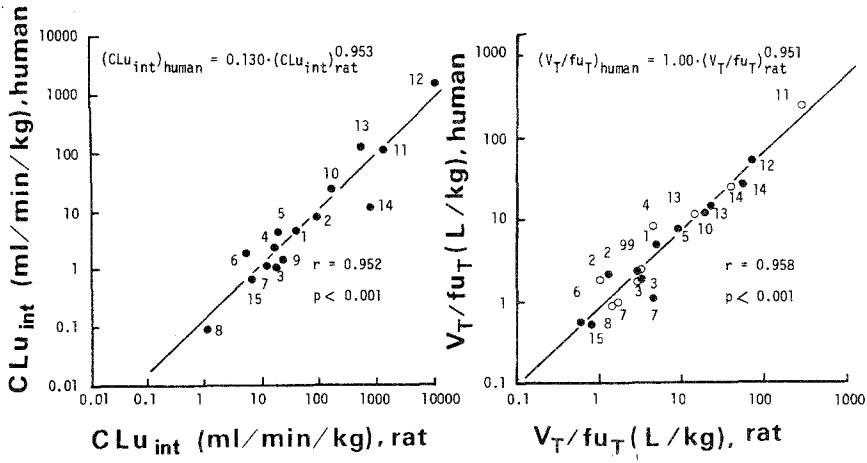

Fig. 3. Correlation between the intrinsic parameters of various drugs in rat and human. Left: metabolic intrinsic clearance of unbound drug; and right: V_T/fu_T for (●) V and (○) V_{ss}. The numbering of the drugs is as in Fig. 1.

were 0.740 and 0.716, and those for the intrinsic parameters in Fig. 3 were 0.906 and 0.918. These findings show that 70% of the variation for the hybridized parameters and 90% of that for the intrinsic parameters in the human can be determined according to the size of the variation for those parameters in the rats. The CLu_{int} of various drugs in the rat were about ten times greater than those in the human. However, little difference was found with regard to V_T/fu_T between rat and human. The correlation coefficient of V_T/fu_T between rat and human was significantly higher than that for V ($p < 0.05$), while there was no significant difference between the correlation coefficients (CLu_{int} vs. CL_m). With regard to data on the protein binding (Cb/Cu), a good correlation was observed (Fig. 4). In spite of high correlations between the intrinsic clearances of unbound drug, unbound volume of distribution of tissues, and plasma unbound fraction (Figs. 3 and 4), relatively poor correlation coefficients between the hybrid parameters, $t_{1/2,z}$, V, and CL_m were obtained (Figs. 1 and 2).

Figure 5 shows the relationships between plasma protein binding (Cb/Cu) and CLu_{int}, and between Cb/Cu and V_T/fu_T. With regard to the relationship between Cb/Cu and CLu_{int}, a statistically significant correlation was not observed. The correlation coefficient between Cb/Cu and V_T/fu_T was low, although it was statistically significant. Boxenbaum (10) reported good correlations between fu_b (blood unbound fraction) and CLu_{int} and between fu_b and V_T/fu_T using benzodiazepine derivatives, and speculated that all three parameters had some common dependence on lipophilicity.

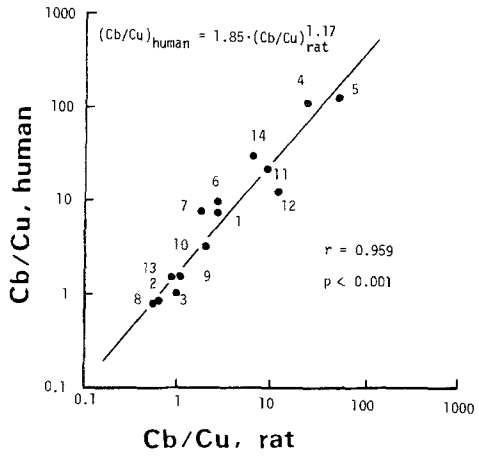

Fig. 4. Correlation between Cb/Cu of various drugs in rat and human. Cb/Cu was calculated by the equation $Cb/Cu = 1/fu - 1$. The numbering of the drugs is as in Fig. 1.

In the present study, pharmacokinetic analysis of both acidic and basic drugs with various kinds of molecular structure was carried out. Acidic drugs such as WA, PBZ, TB, and VA bind strongly to serum albumin (22) and bind weakly to tissue binding components, judging from the values of fu and V_T/fu_T, while DZP binds strongly both to serum albumin and to

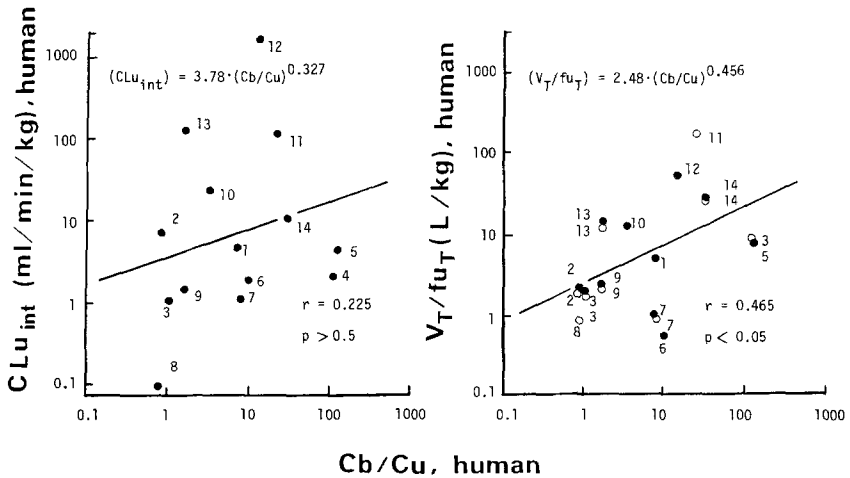

Fig. 5. Relationship between Cb/Cu and intrinsic parameters of various drugs in the human. Left: CL_{int}; right: V_T/fu_T for (●) V and (○) V_{ss}. The numbering of the drugs is as in Fig. 1.

tissue components, due perhaps to its high lipophilicity. Basic drugs such as PL, CPZ, and QD bind not only to albumin, but also to lipoprotein or α_1-acid glycoprotein (23–28), and show an extensive tissue distribution, as judged by a large value of V_T/fu_T. Because of the multiplicity of binding components in plasma and tissues and the heterogeneity in the metabolic enzymes (cytochrome P-450 and UDP-glucuronyltransferase), it is questionable that CLu_{int}, V_T/fu_T, and fu have some common depencence on lipophilicity.

Parameters predicted from the rat are compared to those observed in the human in Table III. The regressive equations in Fig. 3 were used to predict the CLu_{int} and V_T/fu_T in the human. These calculated values were then used in conjunction with fu, Q_H, and V_b in the human, so that predictions could be made for V, CL_m, and $t_{1/2,z}$. As shown in Table III, the predictions for V were successful, with a small absolute percent of error (less than 60%) except for VA. However, the predictions of CL_m for PEB, TB, DZP, and AB showed considerable error, while those of DPH, QD, HXB, PB, WA, CPZ, PL, PEB, VA, AT, and PB were successful, with a small absolute percent of error (less than 56%). With regard to CL_m of DZP, the predicted value was five times larger than that observed. A possible reason for the variations is the difference in the contributions of several metabolic pathways between rat and human.

In the extrapolation of human pharmacokinetic parameters from animal data, the interindividual difference is most important. However, in the case of WA (29, 30), PL (31), QD (32), and DPH (33), a good relationship between V (or CL) and fu (or fu_s, serum unbound fraction) existed. Therefore, V_T/fu_T and CLu_{int} did not show a large interindividual difference and so fu is the primary factor in the interindividual difference in V (or V_{ss}) and CL_m. Thus, interindividual differences do not seem to be a primary cause of variation in the intrinsic parameters.

Another problem is the variation in Q_H. In rats, in the case of high intrinsic clearance (for example, HXB and PTZ) the value of CLu_{int} is changed by 2–4 times by a ±30% change in Q_H. Extrapolation of the rat value to the CL for humans may thus result in a low degree of predictability. On the other hand, drugs with a low CLu_{int} in rats also show a low value of CLu_{int} in humans and therefore values of CL for the rat and the human may be little affected by variations in Q_H.

As shown by Boxenbaum (10) and Sawada *et al.* (11), it is impossible to elucidate interspecies differences in the drug disposition and to predict time courses of plasma drug concentration in the human based on correlations between the apparent $t_{1/2,z}$, CL_m, and V in animal species and in the human. In the present study, interspecies differences in $t_{1/2,z}$, CL_m, and V of acidic and basic drugs may be attributable to differences in fu. Further

Table III. Relationship Between Predicted and Observed Values of Various Pharmacokinetic Parameters in Humans

Drug	V (L/kg)			CL_m (ml/min per kg)			$t_{1/2,z}$ (min)		
	Observed	Predicted	Percent[a]	Observed	Predicted	Percent[a]	Observed	Predicted	Percent[a]
Phenytoin	0.640	0.573	10.5	0.574	0.483	15.9	792	822	3.79
Quinidine	3.20	3.69	22.2	2.91	3.25	11.7	470	785	67.0
Hexobarbital	1.27	0.735	42.1	3.57	4.25	19.0	261	120	54.0
Pentobarbital	0.999	1.57	57.2	0.524	0.964	84.0	1340	1126	16.0
Phenylbutazone	0.122[b]	0.0839[c]	31.2	0.0205	0.0162	21.0	4110	3590	12.7
Warfarin	0.108	0.109	0.926	0.0367	0.0165	55.0	2040	4560	124
Tolbutamide	0.112	0.116	3.57	0.180	0.0589	67.3	434	1360	214
Chlorpromazine	11.2[b]	9.05[c]	19.2	4.29	4.63	7.93	1810	1350	25.2
Propranolol	3.62	3.77	4.14	11.2	15.56	38.9	167	135	19.2
Pentazocine	5.56	7.19	29.3	18.3	11.6	36.6	203	408	101
Valproate	0.151	0.482	219	0.110	0.159	44.5	954	2110	121
Diazepam	0.950	1.44	51.6	0.350	2.13	509	1970	469	76.2
Antipyrine	0.869	0.878	1.04	0.662	0.664	3.02	654	917	40.2
Phenobarbital	0.649	0.817	25.9	0.0530	0.0825	55.7	6600	5870	11.0
Amobarbital	1.04	1.21	16.3	0.556	1.01	81.7	1360	827	39.2

[a] Absolute percent of error.
[b] The value of V_{ss}.
[c] Predicted from the value of V_{ss} in the rat.

study will be necessary to elucidate interspecies differences in the primary processes, i.e., plasma protein binding, intrinsic clearance of unbound drug, tissue distribution of unbound drug, and organ or tissue blood flow and volume, and to predict reliably CL_m, V, and $t_{1/2,z}$ for the human from parameters calculated in experimental animal species. Furthermore, in cases where the effect of blood flow on CL_p cannot be neglected, hepatic and renal blood flows must be determined simultaneously. More precise intrinsic parameters would then be obtained, thereby making it possible to predict more accurately drug disposition in humans from animal data.

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