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The Prediction of Human Pharmacokinetic Parameters from Preclinical and *In Vitro* Metabolism Data

R. SCOTT OBACH, JAMES G. BAXTER, THEODORE E. LISTON, B. MICHAEL SILBER, BARRY C. JONES, FIONA MACINTYRE, DAVID J. RANCE and PHILIP WASTALL

Departments of Drug Metabolism, Pfizer Central Research, Groton, Connecticut (R.S.O., J.G.B., T.E.L., B.M.S.), and Sandwich, Kent (B.C.J., F.M., D.J.R., P.W.), UK

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ABSTRACT

We describe a comprehensive retrospective analysis in which the abilities of several methods by which human pharmacokinetic parameters are predicted from preclinical pharmacokinetic data and/or *in vitro* metabolism data were assessed. The prediction methods examined included both methods from the scientific literature as well as some described in this report for the first time. Four methods were examined for their ability to predict human volume of distribution. Three were highly predictive, yielding, on average, predictions that were within 60% to 90% of actual values. Twelve methods were assessed for their utility in predicting clearance. The most successful allometric scaling method yielded clearance predictions that were, on average, within 80% of actual values. The best methods in which *in vitro* metabolism data from human liver microsomes were scaled to *in vivo* clearance values yielded predicted clearance values that were, on average, within 70% to 80% of actual values. Human $t_{1/2}$ was predicted by combining predictions of human volume of distribution and clearance. The best $t_{1/2}$ prediction methods successfully assigned compounds to appropriate dosing regimen categories (*e.g.,* once daily, twice daily and so forth) 70% to 80% of the time. In addition, correlations between human $t_{1/2}$ and $t_{1/2}$ values from preclinical species were also generally successful (72–87%) when used to predict human dosing regimens. In summary, this retrospective analysis has identified several approaches by which human pharmacokinetic data can be predicted from preclinical data. Such approaches should find utility in the drug discovery and development processes in the identification and selection of compounds that will possess appropriate pharmacokinetic characteristics in humans for progression to clinical trials.

The process by which new drug candidates are discovered and developed is both time consuming and expensive (DiMasi, 1994; DiMasi *et al.*, 1994). This is due in part to the high rate of attrition of drug candidates that enter clinical development, such that only ~10% of drug candidates that are selected for clinical development eventually become marketed drugs. In analyzing the reasons for attrition of drug candidates that enter clinical development, it has been reported that the clinical development of 40% of drug candidates was discontinued due to unacceptable pharmacokinetic properties (Prentis *et al.*, 1988).

These observations strongly suggest that the process by which new drugs are discovered and developed could benefit greatly if drug candidates were advanced to clinical development when predicted human pharmacokinetic characteristics were deemed to be acceptable (*e.g.,* oral bioavailability and duration of exposure are projected to be appropriate for conducting pivotal efficacy studies). Thus, the development and application of reliable methods to predict human drug disposition may decrease the overall attrition of drug candidates during clinical development by decreasing the number of candidates lost due to unacceptable pharmacokinetic characteristics. Furthermore, the eventual clinical utility as well as market success of a newly approved drug could be maximized by selecting for development only those compounds with optimal, rather than acceptable, pharmacokinetic characteristics for the intended therapeutic use.

The best described technique to predict human pharmacokinetics from *in vivo* preclinical pharmacokinetic data is allometric scaling. In its original form, allometry was a technique developed to explain observed relationships between organ size and body weight of mammals (Dedrick *et al.*, 1970; Mordenti, 1986). Additional studies demonstrated further relationships between mammalian body weight and physiological parameters. Considerations of the relationship between drug elimination and physiological parameters such as hepatic or renal blood flow inevitably led to the application of allometric scaling in correlating human pharmacokinetics

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ABBREVIATIONS: f_{ut}, fraction unbound in tissues; f_u, unbound fraction in plasma (or serum); VD_{ss}, steady state volume of distribution (in liters/kg); V_p, plasma volume (in liters/kg), V_e, extracellular fluid volume (in liters/kg); V_r, "remainder of the fluid" volume (in liters/kg); R_e/i, ratio of binding proteins in extracellular fluid (except plasma) to binding proteins in plasma; CL, clearance; F, oral bioavailability; MLP, maximum lifespan potential

with pharmacokinetic parameters in preclinical species (Boxenbaum, 1982, 1984). Allometric scaling of pharmacokinetic data typically focuses on interspecies relationships between clearance or volume of distribution of unbound drug and species body weight; the relationships for these parameters established in preclinical species are then extrapolated to humans, allowing for predictions of human clearance and volume of distribution. Although a number of physiologically rather than allometrically based approaches have also been developed for interspecies scaling of pharmacokinetic data (Iwatsubo *et al.*, 1996; Suzuki *et al.*, 1995), allometry continues to be the most widely used approach due to its simplicity.

In recent years, there has been a resurgence in the use of allometric scaling to establish relationships among preclinical species and humans for both compounds that are metabolically and nonmetabolically cleared (Boxenbaum and DiLea, 1995; Mahmood and Balian, 1995, 1996a, 1996b). The major drawback in allometric scaling is its empirical nature. For example, traditional allometric scaling of plasma clearance does not allow for an understanding of species differences in pathways of metabolic clearance that may have significant impact on the ability to accurately extrapolate human clearance from preclinical data. However, recent publications have proposed novel methods of combining allometric scaling with knowledge of species differences in metabolism derived from *in vitro* metabolism data to improve the utility of allometry for compounds prone to major species differences in metabolism (Lave *et al.*, 1995, 1996a, 1996b; Ubeaud *et al.*, 1995)

Methods by which *in vivo* clearance can be predicted from *in vitro* data were first described ~20 years ago (Rane et *al.*, 1977). The methodologies and mathematics behind approaches to predict *in vivo* clearance from intrinsic clearance data have been summarized in a recent review by Houston (1994). Although the data described by Houston are from rat, the principles described are applicable to other species, including humans (Iwatsubo *et al.*, 1997). In the seminal work by Rane *et al.* (1977), it was demonstrated that the extent of hepatic extraction of several drugs in rats could be estimated from enzyme kinetic parameters of the oxidative biotransformation of these drugs in rat liver microsomes. The concept of an *in vitro/in vivo* correlation that included data from both human and preclinical species was reduced to practice for felodipine 10 years later (Baarnhielm *et al.*, 1986). Various *in vitro* systems are available to obtain hepatic intrinsic clearance data; those most commonly used are liver microsomes, hepatocytes and precision-cut liver slices. Each system possesses unique advantages and disadvantages in both ease of use and accuracy and completeness of the data obtained. In general, for kinetic experiments, such as determination of intrinsic clearance, the body of data available suggest that hepatocytes are a superior method with regard to accurate predictions of *in vivo* data, with microsomes also providing good data (Ashforth *et al.*, 1995; Hayes *et al.*, 1995; Vickers *et al.*, 1993; Zomorodi *et al.*, 1995).

In this article, we describe a comprehensive retrospective analysis of preclinical pharmacokinetic and *in vitro* metabolism data accrued over a 14-year period for Pfizer proprietary compounds. The compounds in the data set used for this analysis cover a broad range of small-molecule (*e.g.,* molecular weight <600) organic compounds designed for therapeutic indications and represents a great challenge to pharmacokinetic prediction methods because each method must not only be applicable to a close-in homologous series of compounds but also be broadly applicable to compounds of all types and physicochemical properties. These data were used in several methods, described herein, designed to predict the pharmacokinetics (clearance, volume of distribution, $t_{1/2}$ and oral bioavailability) of drugs in humans. The methods include a battery of *in vitro*, *in vivo* and combined *in vivo/in vitro* approaches both obtained from the scientific literature and described for the first time here. A comparison of the predicted values to authentic human pharmacokinetic data was made to compare the accuracies and uses of these prediction methods.

Methods

Sources of Pharmacokinetic and *In Vitro* Data

The original pool of compounds included in this analysis were all of those brought into preclinical development at Pfizer over a 14-year period from 1981 through 1994 (n = 83). From this set, those compounds for which no human data were available were removed (n = 30). Another three were excluded because they were developed as prodrugs. Thus, the data used in this analysis included all available preclinical pharmacokinetic and *in vitro* metabolism data for those compounds for which a minimum of a human *in vivo* $t_{1/2}$ value was available (n = 50; table 1). The amount of preclinical data available for each compound ranged from extensive (in which case, all prediction methods could be tested) to scant (in which case, only one or two prediction methods could be applied). Human *in vivo* clearance and oral bioavailability data used for a given compound were from the lowest dose in which sufficient plasma concentration-*vs*.-time data were available to adequately describe the terminal phase. This was done to minimize the potential of including CL and F values that could be confounded by saturation of CL and/or F or limitations on oral absorption at high doses.

Methods for Predicting Human Volume of Distribution

Four methods were examined for their ability to accurately and successfully predict human volume of distribution (table 2): (1) a method in which an average fraction unbound in tissue in preclinical species is used with human plasma protein binding data to calculate human VD_{ss} (method V1), (2) a method in which a proportionality is established between VD_{ss} and f_u in dog and human (method V2) and (3) allometric scaling without (method 3a) and with (method 3b) considerations for interspecies differences in plasma protein binding. This yielded a total of four methods, which are further described below.

Average fraction unbound in tissues method (method V1). In this method, experimentally determined values for volume of distribution (in units of liters/kg) and plasma protein binding for each species were used, along with standard values for extracellular fluid volumes, plasma volumes and so forth, to calculate the fraction unbound in tissues in animal species. The following equation, which is a rearranged form of one previously described by Oie and Tozer (1979), was used to calculate the fraction unbound in tissues for each preclinical species for each compound:

$$f_{ut} = \frac{V_r f_u}{[VD_{ss} - V_p - (f_u V_e)] - \left[(1 - f_u)\frac{R_e}{i} V_p\right]} \quad (1)$$

Table 3 contains the values used for each of these parameters in preclinical species and humans in method V1.

After f_{ut} was calculated for each of the preclinical species, all

TABLE 1
Summary of pharmacokinetic and physicochemical properties of 50 compounds examined[a]

Compound No.	Molecular weight	Acid, base or neutral	Lipophilicity	CL	VD_{ss}	$t_{1/2}$	F	Plasma f_u	Urinary excretion
			clogP	*ml/min/kg*	*liter/kg*	*hr*	*%*		*%*
1	454	Base	6.99			16		0.01	
2	241	Base	2.91			0.9			
3	222	Base	1.48	4.0	0.7	3.5	20	0.12	<2
4	311	Base	3.90			3.8		0.03	
5	412	Base	4.42	12	2.3	2.8	59	0.001	<1
6	296	Base	3.46	15	6.6	4.7	1.0	0.19	<1
7	404	Acid	0.91			1.9		0.51	60
8	380	Base	4.10			7.4		0.07	
9	321	Neutral	5.10			1.2			
10	387	Base	5.97			30			<1
11	339	Acid	4.80			1.3		0.09	
12	262	Neutral	0.62			40		0.55	
13	291	Acid	2.67			5.5		0.02	
14	369	Acid	1.56			2.3		0.01	
15	620	Neutral	4.31			1.5		0.11	
16	740	Neutral	1.83			45			
17	329	Base	0.19	21	1.5	1.1	4.6	0.60	<1
18	327	Base	1.81	16	5.5	4.3		0.60	
19	375	Base	4.37			41		0.08	
20	414	Base	5.50			1.0		0.07	
21	236	Neutral	0.64			43			
22	419	Acid	2.35			27		0.006	
23	749	Base	1.83			68		0.93	6
24	342	Base	5.35			26		0.02	<1
25	320	Acid	4.69	0.1	0.1	26	89	0.001	<2
26	331	Acid	2.70			45		0.007	10
27	338	Acid	4.84			45		0.001	<1
28	452	Base	−0.56			11	70	0.28	10
29	373	Acid	5.59			25		0.005	<1
30	428	Acid	5.53			400		0.005	<1
31	465	Acid	4.61			30		0.01	<1
32	318	Neutral	2.06			2.3		0.08	<1
33	299	Base	6.09			1.0		0.004	<1
34	451	Base	3.82	1.2	1.0	11	69	0.01	<1
35	283	Acid	2.04	7.6	0.4	0.6	70	0.16	47
36	408	Base	2.78	7.0	21.0	35	64	0.03	<1
37	306	Neutral	−0.11	0.3	0.7	26	80	0.89	72
38	283	Acid	4.02			0.9			
39	395	Base	4.00	8.0	15.1	27		0.02	<1
40	253	Base	1.69	3.2	1.5	5.4	93	0.43	20
41	376	Base	1.53	5.9	9.0	2.4		0.02	59
42	441	Base	1.58	4.3	2.8	7.6	83	0.36	65
43	399	Acid	0.18	2.3	3.4	1.6		0.01	61
44	474	Base	2.28	9.8	1.5	4.0	41	0.04	1
45	439	Base	2.03			3.2		0.12	<1
46	418	Base	3.08	5.9	2.1	4.1	46	0.12	8
47	497	Acid	7.21			16		0.001	<1
48	582	Base	5.22			2.5		0.01	
49	415	Base	5.44			33		0.002	
50	426	Base	3.66			3.0		0.08	<1

[a] A blank entry indicates no data available.

value for f_{ut} is assumed to be equal to f_{ut} in humans and, along with the value experimentally determined for human f_u (fraction unbound in human serum/plasma), was used in the prediction of human VD_{ss} (in units of liters/kg) using the following equation (rearranged version of equation 1) and using appropriate human values for V_p, R_e/i and so forth:

$$VD_{(\text{human prediction})} = V_p + [f_{u(\text{human})} \cdot V_e] + \left\{\left[1 - f_{u(\text{human})}\right] \cdot \frac{R_e}{i} \cdot V_p\right\} + V_r \cdot \frac{f_{u(\text{human})}}{f_{ut(\text{average})}} \quad (2)$$

Proportionality (method V2). This method simply states that a plasma in dog and human and the volume of distribution in these two species. [In other words, free $VD_{(human)}$ = free $VD_{(dog)}$.] Implicit to this method was the assumption that tissue binding of drugs is similar in dogs and humans and that physiological parameters, such as extracellular fluid volumes, are similar between the two species on a per-weight basis. Solving for the human volume of distribution (in units of liters/kg) yielded the following equation:

$$VD_{(\text{human prediction})} = \frac{f_{u(\text{human})} \cdot VD_{(\text{dog})}}{f_{u(\text{dog})}} \quad (3)$$

where the term f_u designated the fraction of drug unbound in the plasma (or serum) of dog or human, and $VD_{(\ldots)}$ represented the

TABLE 2
Summary of pharmacokinetic prediction methods

Method	Abbreviation in text	Data required	Underlying assumptions
A. Volume of distributions			
Average fraction unbound in tissues	V1	Plasma protein binding in two or more species and human Intravenous pharmacokinetics in two or more species	Average $f_{ut(preclinical\ species)} = f_{ut(human)}$ R_e/i is uniform across species and is the same for all binding proteins
Dog-human proportionality	V2	Plasma protein binding in dog and human Intravenous pharmacokinetics in dog	$f_{ut(dog)} = f_{ut(human)}$
Allometric scaling, excluding interspecies protein binding differences	V3a	Intravenous pharmacokinetic data in two or more species	No intrinsic differences in plasma protein or tissue binding across preclinical species and human
Allometric scaling, including interspecies protein binding differences	V3b	Intravenous pharmacokinetic data in two or more species Plasma protein binding in two or more species and human	No intrinsic differences in tissue binding across preclinical species and human
B. Clearance			
In vitro $t_{1/2}$, excluding protein binding, well-stirred model	C1a	Turnover rate in human *in vitro* system	*In vitro* rates and activities are representative of those that occur *in vivo* Liver is major organ of CL $CL_{metabolism} \gg CL_{renal} + CL_{biliary}$ Oxidative microsomal metabolism ≫ other metabolism $f_{u(incubation\ matrix)}$ = unity [S] < K_M No inactivation of enzyme Equilibrium not approached
In vitro $t_{1/2}$, including protein binding, well-stirred model	C1b	Plasma protein binding in human Turnover rate in human *in vitro* system	
In vitro $t_{1/2}$, excluding protein binding, parallel tube model	C1c	Turnover rate in human *in vitro* system	
In vitro $t_{1/2}$, including protein binding, parallel tube model	C1d	Plasma protein binding in human Turnover rate in human *in vitro* system	
Enzyme kinetics, excluding f_u, well-stirred model	C2a	Substrate saturation experiment in human *in vitro* system (V_{max}/K_M)	*In vitro* rates and activities are representative of those that occur *in vivo* Liver is major organ of CL $CL_{metabolism} \gg CL_{renal} + CL_{biliary}$ Oxidative microsomal metabolism ≫ other metabolism $f_{u(incubation\ matrix)}$ = unity No inactivation of enzyme
Enzyme kinetics, including f_u, well-stirred model	C2b	Substrate saturation experiment in human *in vitro* system (V_{max}/K_M) Plasma protein binding in human	
Enzyme kinetics, excluding f_u, parallel tube model	C2c	Substrate saturation experiment in human *in vitro* system (V_{max}/K_M)	
Enzyme kinetics, including f_u, parallel tube model	C2d	Substrate saturation experiment in human *in vitro* system (V_{max}/K_M) Plasma protein binding in human	
Allometric scaling, including interspecies f_u and MLP differences	C3a	Plasma protein binding in two or more species and human Intravenous pharmacokinetics in two or more species	Mechanism of CL is similar across species Assumes no interspecies differences in intrinsic CL
Allometric scaling, excluding interspecies f_u differences, including MLP differences	C3b	Intravenous pharmacokinetics in two or more species	
Allometric scaling, including interspecies f_u differences, excluding MLP differences	C3c	Plasma protein binding in two or more species and human Intravenous pharmacokinetics in two or more species	
Allometric scaling, excluding interspecies f_u and MLP differences	C3d	Intravenous pharmacokinetics in two or more species	
C. $t_{1/2}$ and oral bioavailability			
Human *vs.* monkey	T1	Intravenous pharmacokinetics in monkey	Empirical approach; assumes uniform intrinsic properties between preclinical species and humans
Human *vs.* dog	T2	Intravenous pharmacokinetics in dog	
Human *vs.* rat	T3	Intravenous pharmacokinetics in rat	
Combinations of volume and CL predictions	$T_{v(x)c(x)}$	Data for particular CL and volume prediction methods	Same assumptions for individual VD and CL prediction methods VD_{ss} prediction inappropriate for $t_{1/2}$ prediction if multicompartmental pharmacokinetic behavior is anticipated
Corresponding CL methods	$F_{c(x)}$	Data for particular CL methods	Same assumptions for individual CL prediction methods Fraction absorbed is unity and no first-pass

TABLE 3
Values used for physiological constants in selected preclinical species and humans

Species	V_p	V_e	V_r	R_e/i[a]	Body weight	$\log_{10}$ body weight	MLP
		liters/kg			*kg*		*years*
Mouse	N.A.	N.A.	N.A.	N.A.	0.02	−1.70	2.7
Rat	0.0313	0.265	0.364	1.4	0.25	−0.60	4.7
Guinea pig	0.0313	0.265	0.364	1.4	0.5	−0.30	6.7
Rabbit	0.0314	0.179	0.322	1.4	3.0	0.48	8.0
Monkey	0.0448	0.208	0.485	1.4	3.5	0.54	20
Dog	0.0515	0.216	0.450	1.4	12.5	1.10	20
Human	0.0436	0.151	0.380	1.4	70	1.84	93

Some values were from Davies and Morris (1993) and Oie and Tozer (1979).
NA, not available.
[a] R_e/i was assumed to be 1.4 for all species and all binding proteins.

Allometry without protein binding (method V3a). In allometric scaling of volume of distribution, the physiological parameter used in the scaling was total body weight (Boxenbaum, 1982). In this method, plots were constructed of total volume of distribution in preclinical species (in units of liters per animal) *vs.* animal body weight (table 3) on a log-log scale for each compound in the analysis. Allometric equations in the form:

$$\log_{10}\mathrm{VD} = a \cdot \log_{10}\text{body weight}_{(\mathrm{kg})} + b \tag{4}$$

were obtained by linear regression of the data points to determine the values a and b for each compound. These were then used, along with a standard value for human body weight (70 kg), to predict human volumes of distribution.

Allometry corrected for protein binding (method V3b). An identical approach was taken as described above except that animal volume of distribution values were corrected for plasma protein binding using the following equation:

$$\mathrm{VD}_{\mathrm{free}} = \frac{\mathrm{VD}_{\mathrm{total}}}{f_u} \tag{5}$$

to yield free volumes of distribution. These values were then plotted as in method V3a to determine the allometric relationship for free volume of distribution *vs.* total body weight. The projected human free volume of distribution was then converted to total volume of distribution by $\mathrm{VD}_{\mathrm{free(human)}} \cdot f_{u(\mathrm{human})}$.

Methods for Predicting Human Clearance

Three approaches were examined for their ability to accurately and successfully predict human CL, with each approach possessing important variations, leading to a total of 12 prediction methods (table 2): (1) methods in which first-order consumption of parent drug was monitored in liver microsomal incubations to yield *in vitro* $t_{1/2}$ values (methods C1a–C1d), (2) methods in which V_{max} and K_{Mapp} were determined and used in the calculation of CL'_{int} (methods C2a–C2d) and (3) allometric scaling methods with and without considerations of interspecies differences in plasma protein binding and/or MLP (methods C3a–C3d).

***In vitro* $t_{1/2}$ methods.** With methods C1a, C1b, C1c and C1d, values for intrinsic CL (CL'_{int}) were calculated from *in vitro* $t_{1/2}$ data obtained in an appropriate system (*e.g.,* liver microsomes), which were then scaled up to represent the CL expected in an entire organism. The fundamental basis behind this simple approach lies in the derivation of the integrated Michaelis-Menten equation (Segel, 1975):

$$\frac{K_{\mathrm{Mapp}} + [\mathrm{S}]}{\quad}$$

Over one $t_{1/2}$ (*i.e.*, when $[\mathrm{S}] = 0.5[\mathrm{S}]_{t=0}$, the following equation applies:

$$\frac{V_m \cdot t_{1/2}}{K_{\mathrm{Mapp}}} = 0.693 + \frac{0.5[\mathrm{S}]_{t=0}}{K_{\mathrm{Mapp}}} \tag{7}$$

A necessary assumption in this approach, which is included in the experimental design, is that the substrate concentration used is well below the K_{Mapp} value, such that:

$$\frac{0.5[\mathrm{S}]}{K_{\mathrm{Mapp}}} \ll 0.693 \tag{8}$$

Thus, the equation degenerates to:

$$\frac{V_m \cdot t_{1/2}}{K_{\mathrm{Mapp}}} = 0.693 \tag{9}$$

$$\frac{V_m}{K_{\mathrm{Mapp}}} = \frac{0.693}{t_{1/2}} = CL'_{int} \tag{10}$$

The *in vitro* $t_{1/2}$ is incorporated into the following equation:

$$CL'_{int} = \frac{0.693 \cdot \text{liver weight}}{\textit{in vitro } t_{1/2} \cdot \text{liver in incubation} \cdot f_{u(inc)}} \tag{11}$$

where *in vitro* $t_{1/2}$ is in min, liver weight is in g/kg of body weight and liver in incubation refers to the g of liver/ml in the incubation, resulting in units of ml/min/kg for CL'_{int}. The "liver in incubation" value was calculated from the amount of protein in the incubation and a scale-up factor from protein to g of liver. [For microsomes, this scale-up factor is 45 mg/g of liver (Houston, 1994).] This equation indicates that a value for binding to protein in the incubation be included, however, in this treatment, it was assumed to be zero (*i.e.,* $f_{u(inc)} = 1$; see Discussion). Thus, the intrinsic CL values calculated were based on total concentrations, not free concentrations in the incubation. Full expansion of equation 11 yields the following:

$$CL'_{int} = 0.693 \cdot \frac{1}{t_{1/2}(\mathrm{min})} \cdot \frac{\text{g of liver weight}}{\text{kg of body weight}} \cdot \frac{\text{ml incubation}}{\text{mg of microsomal protein}} \cdot \frac{45\text{mg of microsomal protein}}{\text{g of liver weight}} \tag{12}$$

Conversion of intrinsic CL to CL involved the use of equations describing the well-stirred (equation 13) and parallel tube (equation 14) models of hepatic CL (Pang and Rowland, 1977; Wilkinson and Shand, 1975):

$$CL_p = \frac{Q \cdot f_u \cdot CL'_{int}}{Q + f_u \cdot CL'_{int}} \tag{13}$$

$$CL_p = Q \cdot \left(1 - e^{\frac{-CL_{int} \cdot fu}{Q}}\right) \tag{14}$$

where Q is hepatic blood flow, and f_u is the free fraction in blood. Values of 20 ml/min/kg for hepatic blood flow and 20 g of liver/kg of body weight were used in these calculations. Also, when the blood/plasma ratio was known to significantly differ from unity, plasma (or serum) CL values were converted to blood CL values by correcting with the blood/plasma ratio:

$$\frac{CL_p}{\quad}$$

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