Elucidation of Human Amphotericin B Pharmacokinetics: Identification of a New Potential Factor Affecting Interspecies Pharmacokinetic Scaling

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Purpose. To elucidate the pharmacokinetics of amphotericin B in rats, mice and humans, and to perform interspecies scaling to humans using allometry.

Methods. Plasma concentrations following intravenous bolus administration in rats, and mice were determined by HPLC. Human pharmacokinetic parameters elucidated from literature data were validated in a preliminary study involving a patient receiving daily infusion dose for 27 days. A critical literature review was conducted to identify appropriate pharmacokinetic parameter values in other species for interspecies scale-up. Interspecies allometric scale-up was performed across mice, rats, rabbits and dogs and the resulting predictions in humans were compared to observed values.

Results. A triexponential decline in rat, mouse and human plasma concentrations were observed. No gender differences in rat pharmacokinetics were observed. In contrast to allometry, mouse CL was smaller (82 vs 116 ml/h/kg) and $T_{0.5}$ (33 vs 20 h) was longer compared to rat. In the preliminary human study, Cpeak and Cmin values remained relatively constant over the duration of therapy, and a CL, MRT, $T_{0.5}$, Vss and Vdarea of 26 ml/h/kg, 10 and 23 days, 6.2 and 20 L/kg, respectively, were estimated. The relative contributions of the terminal phase area in rat, mouse and human were 75%, 92% and 31%, respectively. Interspecies allometric scale-up predictions of human CL (41 ml/h/kg), CLu (467 ml/h/kg) and Vss (3.3 L/kg) were similar to reported values, whereas poor predictions of human Vuss (33 L/kg), Vdarea (4.1 L/kg) and $T_{0.5}$ (3 days) were obtained.

Conclusions. Insignificant accumulation in humans inspite of the long terminal $T_{0.5}$ was rationalized to be due to the small terminal-phase area contribution. While human CL and Vss were sucessfully predicted in the interspecies scaling, poor predictions of human Vdarea and $T_{0.5}$ were obtained, which was attributed to disposition pattern differences between humans and other species, a potential new critical factor affecting interspecies scale-up.

KEY WORDS: amphotericin B; pharmacokinetics; human; gender-differences; disposition function differences; interspecies scaling.

INTRODUCTION

Amphotericin B is the drug of choice in the treatment of invasive fungal diseases (1). Although widely used in humans for the past 40 years, its pharmacokinetics have not been completely elucidated (1). For example, reported mean total plasma clearance (CL) varied from 10 to 202 ml/h/kg (2,3) and mean terminal half-life ($T_{0.5}$) from about 10 to 366 h (4,5). Further compounding this problem is the large variability in reported animal data. For example, among seven studies in rats (6–12) (Table I), mean CL ranged from 158 to 290 ml/h/kg (12,7), steady-state volume of distribution (Vss) from 2.6 to 24.1 L/kg (10,7) and $T_{0.5}$ from 8.7 to 20 h (10,7). In mice $T_{0.5}$ from 11 to 28 h (13,12), in rabbits CL from 39 to 197 ml/h/kg (14,15), in dogs $T_{0.5}$ from 47 to 93 h (12,16) and in monkeys $T_{0.5}$ from 35 to 275 h (12,17) have been reported. These variabilities probably contributed to the poor prediction of human pharmacokinetic parameters reported in a recent (18) intersepecies scaling to humans based on four species (mice, rats, dogs and monkeys).

The main purpose of the present study is to elucidate the pharmacokinetics of amphotericin B in rats, mice and humans, and to perform interspecies scale-up to humans using rat and mouse values from the present study and, rabbit and dog values obtained from a review of the literature. Plasma protein binding studies in five species were conducted and interspecies scale-up of unbound clearance (CLu) and unbound volume of distribution (Vuss) were also explored. Additionally, gender as a source of variability in rats was studied since most earlier rat studies (6–10,12) were conducted in males.

MATERIALS

Amphotericin B for injection USP (Pharmacia Inc., Albuquerque, NM) and 5% dextrose injection USP (Baxter, Deerfield, IL) were obtained commercially. HPLC grade sodium acetate and acetic acid were obtained from Fisher Scientific (Itasca, IL). Human plasma was donated by the University of Illinois Hospital Blood Bank.

METHODS

Intravenous Kinetic Studies in Male and Female Rats

Five male (296 ± 10 g) and 5 female (220 ± 6 g) Sprague-Dawley rats (Harlan Sprague-Dawley Inc. Indianapolis, IN) were anesthetized with Ketalar® (ketamine HCl) and Tranquived® (xylazine HCl), administered intramuscularly. The right jugular vein and right carotid artery were cannulated for intravenous dosing and for blood sampling, respectively. Following bolus administration of either 1.0 or 1.5 mg/kg to female rats and 1.0 mg/kg to male rats, serial blood samples (0.25 ml) were obtained at 5 min, 0.5, 2, 4, 8 h and at approximately 12 hour intervals thereafter until 120 h after dosing via the carotid artery or by cardiac puncture when the arterial cannula clogged. Samples were centrifuged and the separated plasma was used for HPLC analysis.

Intravenous Kinetic Studies in Mice

Amphotericin B (1.0 mg/kg) was administered via the tail vein to sixty-four Swiss Webster mice (18 to 25 g) of either sex obtained from Harlan Sprague-Dawley Inc. Blood samples were collected via cardiac puncture from groups of four or five mice at each of the following times after dosing: 0.083, 0.5, 1, 2, 4, 6, 9, 12, 15, 18, 24, 30, 36, 48, 72 and 96 h. Samples were centrifuged and plasma was used for HPLC analysis.

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Table I. Reported Pharmacokinetic Values of Amphotericin B in Rats

Study	Dose (mg/kg)	CL (ml/h/kg)	$T_{0.5}$ (h)	Vss (L/kg)	Vdarea (L/kg)
Chow (1995)	0.38	211 (193)	12.8	3.3	4.4
	1.32	235 (281)	17.2	5.8	5.9
	4.21	242 (229)	14.4	3.3	5.3
Wang (1995)	1.0	290	19.7	24	
Chow (1992)	0.28	257	9.7	3.5	3.6
	0.45	230	10.1	3.2	3.4
	0.84	235	11.5	3.8	3.9
Fielding (1991)	1.0	260	10.4	4.3	3.8
Wasan (1990)	0.8	198	8.7	2.6	
Vadei (1990)	1.2	177	17.3	4.2	
Kim (1984)	0.6	158	16.0		

Note: Values in parentheses were obtained from steady-state concentrations.

Plasma Protein Binding Study

Amphotericin B protein binding in pooled mouse, rat, rabbit, dog and human plasma was determined by equilibrium dialysis (concentration range: 0.4–1.6 μg/ml) conducted at 37°C for 96 hours (19) using a SpectraPor® 12,000–14,000 membrane (Spectrum Medical Industries, Los Angeles, CA). The fraction unbound was calculated by the standard method (20).

HPLC Analysis

HPLC method of Golas et al (21) was slightly modified for the determination of amphotericin B concentrations in plasma. To 100 μl of plasma was added 200 μl of acetonitrile: methanol (75:25) mixture. The microcentrifuge tubes were vortexed and centrifuged. 200 μl of the resulting supernatant was injected into a C_{18} μ-Bondapak (3.9 × 300 mm, 10 μ) column (Waters Associates, MA) by a Waters 717 plus autosampler. The mobile phase consisting of 0.1 M sodium acetate buffer (pH 5.5) and acetonitrile (53:47) was pumped using a Waters 600E multisolvent delivery system at a flow rate of 1.6 ml/min and the eluting peaks detected at 405 nm using a Waters 996 photodiode array detector. A limit of quantification of 5 ng/ml was obtained under the conditions described above with a coefficient of variation of less than 6 %.

Pharmacokinetic Analyses

The area under the curve (AUC) was estimated by the log-linear trapezoidal rule, recommended by Chiou (22). CL, CLu, Vss, Vuss, mean residence time (MRT) and terminal distribution volume (Vdarea) were calculated according to standard methods. PCNONLIN (SCI software, Lexington, KY) was used to perform nonlinear regression and, the coefficients and exponents thus obtained were used to calculate the initial volume of distribution (V_0). Model discrimination was based on Akaike information and Schwartz criteria. The contribution of each exponential phase was also estimated (23). The mean values of CL, $T_{0.5}$ and volume terms were calculated by the harmonic mean method (24,25). Mean concentrations were used for pharmacokinetic analysis in mice.

Allometric method (26) was employed for interspecies scaling of CL, CLu, Vss, Vuss, Vdarea and $T_{0.5}$, from four different animal species to humans. Humans were not included in the regression analysis.

RESULTS AND DISCUSSION

Present Rat Study

Plasma level profiles in both male and female rats after an intravenous bolus injection are depicted in Fig. 1 and the pharmacokinetic parameters calculated are summarized in Table II. No statistically significant gender differences in any of the calculated parameters were found although mean CL in males was slightly higher (122 vs 111 ml/h/kg). Dose and body weight normalized AUC in the female study of 9314 and 8667 ng · h/ml for the 1.0 and 1.5 mg/kg dose, respectively, were essentially identical. Therefore, all parameters from the 10 rats studied were pooled together (Table II) in subsequent discussions.

The plasma concentration profiles seem to best fit a tri-exponential equation with a mean alpha, beta and gamma half-life of 0.16, 1.4 and 20.3 h. The mean contributions of these phases to the total AUC were 9, 16 and 75%, respectively. The mean CL and MRT were 116 ml/h/kg and 20.1 hours, respectively. The mean V_0, Vss and Vdarea were 0.30, 2.3 and 3.4 L/kg, respectively.

Comparison with Earlier Rat Studies

Mean CL of amphotericin B in earlier studies (Table I) were 36% (12) to 150% (7) higher than the 116 ml/h/kg observed in this study (Table I) (6–12). The higher CL reported in earlier studies could be attributed to the lack of early blood sampling (first sample usually collected at 0.5 h) and the consequent biexponential characterization of rat plasma profiles (6–12). However, this would only result in an approximately 10% difference in CL between the present and earlier studies because of the minor (9%) alpha-phase area contribution to the total AUC. The alpha-phase concentration, however, cannot be ignored because of the relationship between initial high plasma

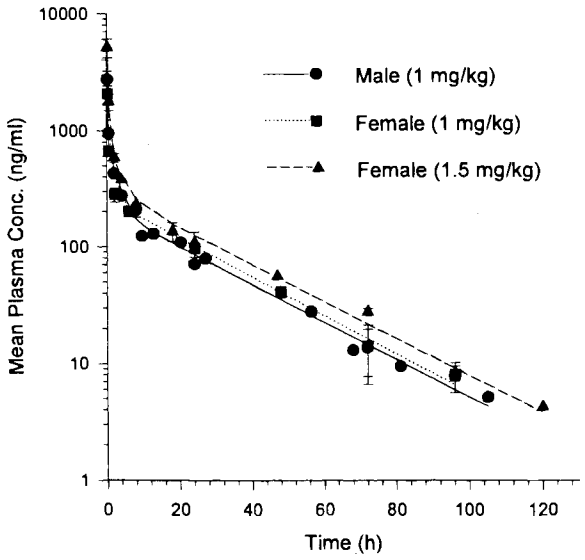

Fig. 1. Amphotericin B plasma concentrations in male and female Sprague-Dawley rats following intravenous bolus administration.

Table II. Pharmacokinetic Parameters Obtained Following Administration of an Intravenous Bolus Dose of Either 1.0 or 1.5 mg/kg Amphotericin B in Male and Female Rats

Group	AUC (ng · h/ml)	CL (ml/h/kg)	$T_{0.5}$ (h)	MRT (h)	V_0 (L/kg)	Vss (L/kg)	Vdarea (L/kg)
Female (n = 5)	9055 ± 864.5	111 ± 10.0	20.3	20.3 ± 2.71	0.30 ± 0.08	2.2 ± 0.43	3.2 ± 0.58
Male (n = 5)	8207 ± 947.4	122 ± 14.2	20.4	20.0 ± 1.93	0.27 ± 0.07	2.4 ± 0.17	3.6 ± 0.68
Pooled (n = 10)	8631 ± 1011	116 ± 13.7	20.3	20.1 ± 2.49	0.28 ± 0.08	2.3 ± 0.36	3.4 ± 0.70

amphotericin B concentrations obtained following bolus intravenous dosing and the cardiotoxicity in animals and man (27).

Another possible reason for the higher CL in the previous studies could be early termination of sampling during the terminal phase resulting in the estimation of a shorter $T_{0.5}$ and a smaller extrapolated area. For example, in the study by Wasan et al. (10) the last sample was collected at 24 hours, which time is probably insufficient to accurately estimate the long $T_{0.5}$, thus resulting in the estimation of the shortest reported $T_{0.5}$ for amphotericin B in rats (8.7 h) and a higher clearance (198 ml/h/kg). It is clear that although the concentration of amphotericin B declines to approximately one-tenth its initial value by 24 hours, the contribution of the extrapolated area from 24 hours to infinity is still very significant because of the dominant terminal phase.

Interestingly, a smaller CL of 139 ml/h/kg is obtained upon reanalysis of data of Fielding et al. (9) using trapezoidal rule as compared to the reported CL of 260 ml/h/kg which was obtained by curve fitting. Moreover, when an initial concentration and $T_{0.5}$ (for extrapolation) from the present study were used, the resulting CL, MRT, Vss and Vdarea of 107 ml/h/kg, 23 h, 2.5 L/kg and 3.1 L/kg are almost identical to the values obtained in our study, probably further validating our results.

Based on the above analyses and discussion, it is postulated that the parameters obtained in our rat study may more closely represent the true values in rats and are therefore chosen for later interspecies scale-up or correlation.

Present Mouse Study

The observed plasma concentrations in mice seem to best fit a tri-exponential equation with an alpha, beta and gamma half-life of 0.22, 1.7 and 33 h, respectively (Fig. 2). The disposition equation was Cp (ng/ml) = 1900 ($e^{-3.1*t}$) + 140 ($e^{-0.41*t}$) + 226 ($e^{-0.021*t}$) (rate constants = h^{-1}), with a large gamma-phase area contribution of 92%. Contrary to allometric expectation, a smaller CL of 82.5 ml/h/kg and a longer $T_{0.5}$ of 33 h and MRT of 41 h, compared to rats, were calculated, whereas V_0, Vss and Vdarea of 0.44, 3.4 and 3.9 L/kg were similar to rats.

The results obtained in the present study are similar to those of Kim et al. (12) although a bi-exponential decline in plasma concentrations was reported by them. Therefore, CL, Vss, $T_{0.5}$, and Vdarea values from the present study and from Kim et al. (12) were used for subsequent interspecies scaling.

Elucidation of Human Pharmacokinetics

Of the few pharmacokinetic studies of amphotericin B in humans reported in the literature, Chabot et al. (2) and Atkinson and Bennett (5) are often referenced. Although, a similar Vss of 3.2–4.0 L/kg and a long $T_{0.5}$ of 11–15 days are reported (2,5) by both studies, yet the CL, MRT and Vdarea, of 10 ml/h/kg, 12 days and 3.8 L/kg, respectively, of Chabot et al. (2) are very different from the CL of 26 ml/h/kg and estimated MRT of 6.5 days and Vdarea of 14 L/kg, of Atkinson and Bennett (5).

The similarity between MRT and $T_{0.5}$, and between Vss and Vdarea of Chabot et al. (2) suggest a predominant terminal phase in the disposition function—implying substantial accumulation and the attainment of steady-state following weeks of therapy in humans. However, contrary to the above expectation, following continuous infusion for five consecutive days, an initial rapid rise in plasma concentrations during the first day and insignificant accumulation thereafter were observed in most of the 14 patients in their study (2). A similar observation of insignificant accumulation over 1–3 weeks following daily dosing was documented in other studies (28,29) as well.

Contrary to Chabot et al. (2), the parameters reported from Atkinson and Bennett (5) imply insignificant accumulation upon multiple dosing; a MRT less than one-half of the $T_{0.5}$ and a Vdarea three-fold larger than Vss suggest a relatively small terminal-phase area contribution to the total AUC. As expected, a mean terminal gamma-phase area contribution of only 27% was calculated, while the beta-phase with a half-life of 17 h was the major phase with a mean contribution of 65% for the patients of Atkinson and Bennett (5). Using the plasma area method of Chiou (23), 70% of steady-state is predicted to be achieved within 48 hours followed by gradual but minimal increases in trough concentrations thereafter.

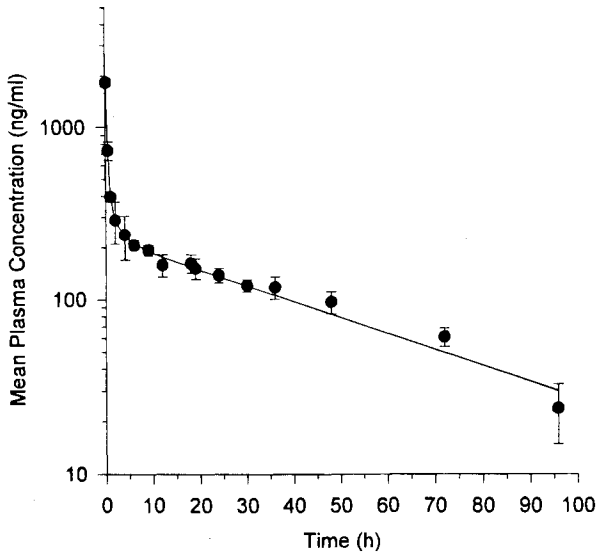

Fig. 2. Mean plasma concentrations in mice following intravenous bolus administration of amphotericin B (1 mg/kg).

A similar trend of insignificant accumulation and minor contribution of the gamma-phase area (31%) was confirmed by the present authors in an HIV-positive patient (56 kg) (protocol approved by IRB and informed consent obtained) receiving amphotericin B: 16 mg on day 1, 40 mg on days 2–16, and 50 mg on days 17–27 (Fig. 3). The calculated CL, MRT, $T_{0.5}$, Vss and Vdarea of 25.5 ml/h/kg, 10 days, 23 days, 6.2 and 20 L/kg, respectively, were similar to those reported by Atkinson and Bennett (5).

The above rationale seems to explain the similar CL values of 26 ml/h/kg (4) and 29 ml/h/kg (30) obtained by other investigators although a much shorter $T_{0.5}$ of 10 h (4) or 18 h (30) was employed. Also, CL estimation based on an assumption of having reached steady-state in the first week of therapy (29) would result in minimal overestimation of CL. Therefore, pharmacokinetic parameters from Atkinson and Bennett (5) and additionally, CL from the above studies (4,29,30) were used for comparison of predictions in humans in the present interspecies scale-up.

Evaluation of Earlier Studies in Other Species

Rabbits

The CL of 43 ml/h/kg calculated from an average steady-state (day 28) concentration of 0.97 μg/ml from Lee et al. (14) was used for interspecies scaling in the present study. The CL of 51 ml/h/kg reported by Bouley et al. (31) was not used because of absence of sampling until the first hour following cessation of infusion. However, a $T_{0.5}$ of 31.4 h obtained from reanalysis of the reported mean terminal concentrations and, Vss and Vdarea calculated from reported mean data by Bouley et al. (31) in rabbits were used in the present interspecies scaling. The $T_{0.5}$ values of 12.7 to 18.3 h estimated following a single bolus administration in rabbits by Lee et al. (14) were not selected for interspecies scaling since, multiple dose data in the same study (14) showed a continued rise in plasma concentrations beyond 3 days suggesting a longer $T_{0.5}$. Hutchaleelaha et al. (18) did not employ rabbits in their interspecies scaling study; the reason for this is unclear.

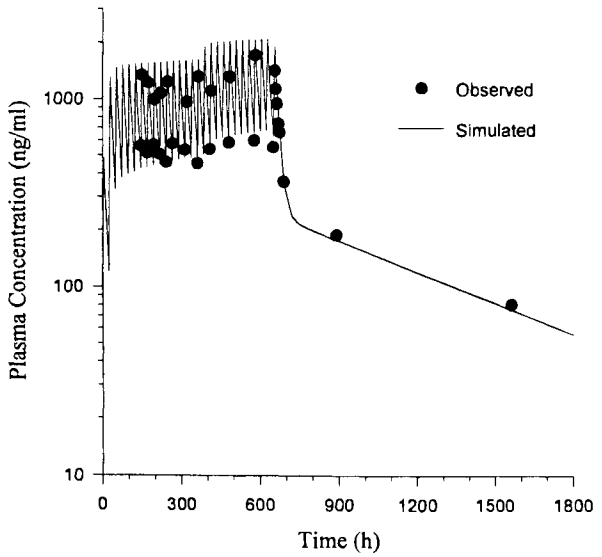

Fig. 3. Plasma concentrations in a patient receiving short-term infusions of amphotericin B daily for 27 days. Filled circles: observed concentrations; solid line: simulated concentrations.

Dogs

In the present interspecies scaling, nearly identical CL of 54.5 and 53.0 ml/h/kg in dogs reported by Kim et al. (12) and Fielding et al. (32), respectively, and a slightly lower CL of 40.8 ml/h/kg by Craven et al. (16) in larger dogs (20.3 kg), were employed.

The mean $T_{0.5}$ of 92.6 h (harmonic mean), Vss and Vdarea from Craven et al. (16) were used for interspecies scale-up. The multiple dose data of Fielding et al. (32) implies a $T_{0.5}$ of about 90 h in dogs, which validates the $T_{0.5}$ reported by Craven et al. (16) but is much larger than the 46.8-h $T_{0.5}$ reported by Kim et al. (12).

Monkeys

The paucity of amphotericin B pharmacokinetic data and the striking differences in the parameter values reported by the only two studies (12,17) in monkeys resulted in their exclusion from the present interspecies scaling. For example, although, 96 h sampling was performed by both Kim et al. (12) and Jagdis et al. (17), yet strikingly different CL and $T_{0.5}$ values of 28.4 ml/h/kg and 35.3 h and, 10.2 ml/h/kg and 275 h, respectively, were reported. Hutchaleelaha et al (18) used monkey CL and $T_{0.5}$ values of 21 ml/h/kg and 56 h, respectively, which were obtained from reanalysis of data of Jagdis et al. (17).

Amphotericin B Plasma Protein Binding

Amphotericin B concentrations between the donor and receiver compartments reached equilibrium by 96 h in the dialysis study. Mean percent unbound values of 7.4, 11, 9.0, 8.5 and 5.2% in mouse, rat, rabbit, dog, and human plasma, respectively, were estimated. These values were subsequently used in the estimation of respective CLu and Vuss values (Table III). The fraction unbound obtained with human plasma is consistent with a previous study (19).

Interspecies Scaling of Amphotericin B Pharmacokinetics to Humans

Allometry has been used in the extrapolation of pharmacokinetic parameters across species (26). In the present scaling, predicted CL of 41 ml/h/kg (based on 70 kg human) obtained by simple allometry $(63.3\ (BW)^{0.90};\ r^2 = 0.992)$ (Fig. 3), although slightly higher, is similar to reported CL values (4,5,32,33). On the contrary, an underestimated CL prediction of 12.8 ml/h/kg $(4480.2\ (BW)^{1.2};\ r^2 = 0.992)$, which is similar to that of Chabot et al. (2) (10 ml/h/kg), was obtained using the maximum lifespan potential (MLP) approach (Fig. 3).

Also, an accurate Vss prediction of 3.3 L/kg $(2.98\ (BW)^{1.03};\ r^2 = 0.986)$ was obtained as compared to the reported value of 4.0 L/kg (5). Our results seem to be in sharp contrast with those of Hutchaleelaha et al. (18), where, a five-fold smaller CL of 7.4 ml/h/kg and three-fold smaller Vss of 1.2 L/kg were predicted. Interestingly, the omission of mice because of its apparent non-allometric behavior and subsequent scaling across only three species results in an accurate CL prediction

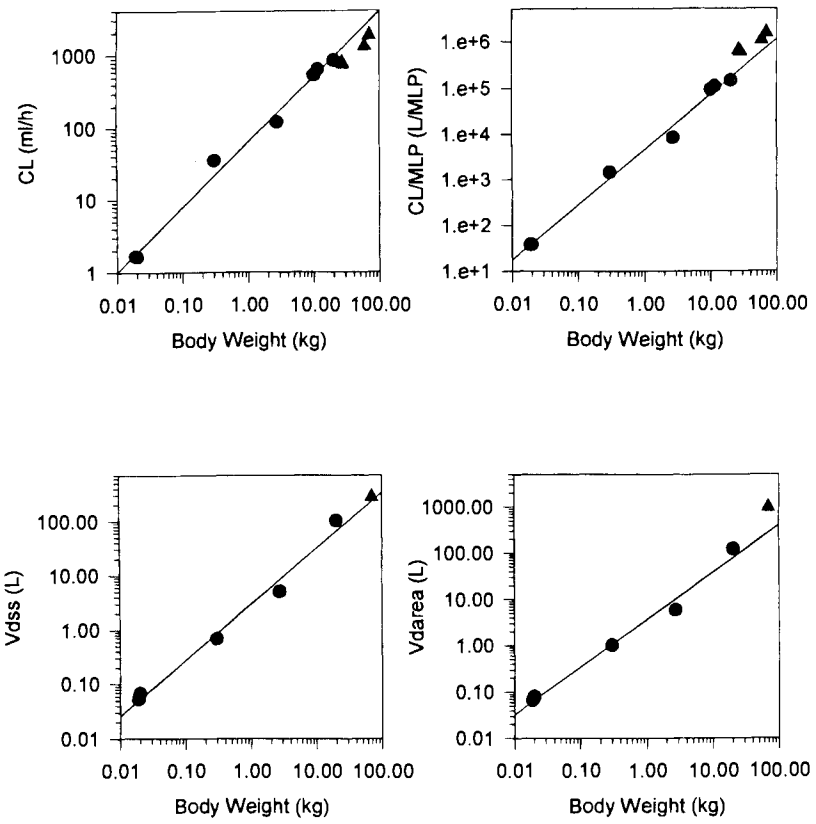

Fig. 4. Interspecies scaling of CL, CL/MLP, Vss and Vdarea of amphotericin B across four animal species to humans using allometry. Filled circles: mouse, rat, rabbit and dog; filled triangles: human.

of 31.9 ml/h/kg (77.9 $(BW)^{0.79}$; $r^2 = 0.972$) in humans, while the prediction (12.0 ml/h/kg, 4719.5 $(BW)^{1.8}$; $r^2 = 0.964$) did not improve by the MLP approach.

The predicted Vdarea of 4.1 L/kg (3.7 $(BW)^{1.02}$; $r^2 = 0.987$) is much smaller than the reported value of 13.9 L/kg (5). Such a failure of prediction can be rationalized by a much smaller contribution of the terminal phase area in humans compared to other species. This difference in the relative contribution of the terminal-phase area between species appears to be a critical factor in Vdarea correlation or scale-up, which is contrary to conventional physiological modeling and has not been discussed in the literature to date. Similarly, this factor is postulated to partially account for the failure in predicting human $T_{0.5}$ (3 vs. 11–15 days (2,5)) (39.9 $(BW)^{0.13}$; $r^2 = 0.45$).

Simulation studies were performed, by fixing human CL, Vss and MRT and varying the intercompartmental transfer rate constants, in an attempt to identify potential reasons for the similar CL and Vss, but dissimilar $T_{0.5}$ and Vdarea seen between

Table III. Amphotericin B Pharmacokinetic Values in Different Species Used for Allometric Analysis

Species	Body weight (kg)	CL (ml/h)	% free	CLu (ml/h)	$T_{0.5}$ (h)	Vss (L)	Vuss (L)	Vdarea (L)	Reference
Mouse	0.019	1.652	7.4	19.518	27.5	0.054	0.730	0.066	12
	0.020	1.649		19.483	33.0	0.068	0.919	0.079	Present Study
Rats	0.30	34.77	11	299.74	20.3	0.690	5.948	1.02	Present Study
Rabbits	2.75	118.3	9.0	1314.4					14
	2.75				31.4	5.10	56.67	5.92	31
Dog	11.5	627.3	8.5	7369.6					12
	10.0	530.0		6226.5					32
	20.3	828.2		9729.8	92.6	102	1200	123	16
Human	69.8	1803	5.2	34673	366	280	5385	968	5
	70.0				264				2
	28.0	728.0		14000					4
	56.2	1281		24635					29
	26.8	771.6		14838					30

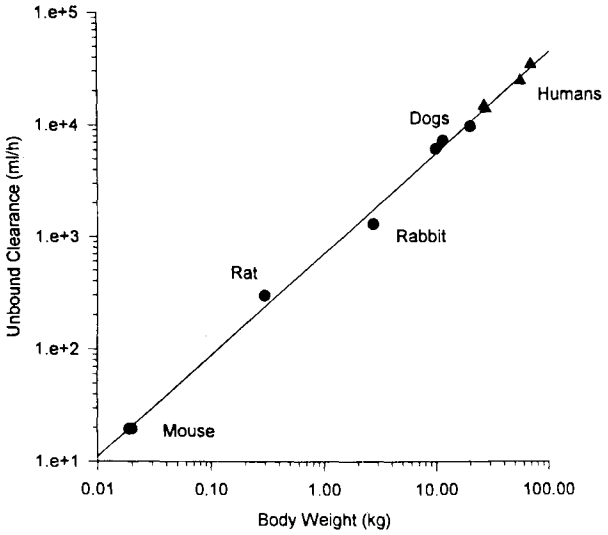

Fig. 5. Interspecies scaling of CLu of amphotericin B across four animal species to humans using allometry. Filled circles: mouse, rat, rabbit and dog; filled triangles: human.

species. An approximately nine-fold slower entry and exit rate constants across the slowly equilibrating compartment was shown to result in a small terminal-phase area contribution in humans. The reason for the slower uptake and release from the peripheral compartment in humans compared to other species can be postulated to be due to distribution into other peripheral tissues, differences in binding sites/kinetics or due to other reasons.

Use of unbound plasma clearance of drugs has been shown to improve interspecies correlation or prediction (20 and references therein). The predicted human CLu of 467 ml/h/kg (707 $(BW)^{0.90}$; $r^2 = 0.996$) (based on 70 kg) is very similar to observed CLu of 497 ml/h/kg (5) and other studies (4,32,33) (Fig. 5). An underestimated prediction of human Vuss of 33 L/kg (33.64 $(BW)^{1.0}$; $r^2 = 0.975$) compared to the observed value of 77 L/kg (5) was obtained. Although improvement in prediction using the unbound vs. total CL approach was not very marked, the study of interspecies relationship of CLu could be useful when using animal models to study amphotericin B induced nephrotoxicity.

In conclusion, the pharmacokinetics of amphotericin B in rats, mice and humans were elucidated. Simple allometry was successfully employed to predict human CL, CLu and Vss based on data from four animal species. The presence of dissimilarity in relative contribution of the terminal phase area between humans and other species was identified and its effect on the interspecies scale-up was presented. Whether this factor is partially responsible for the failure of interspecies scale-up of other drugs remains to be studied.

REFERENCES

1. M. P. Nagata, C. A. Gentry, and E. M. Hampton. Is there a therapeutic or pharmacokinetic rationale for amphotericin B dosing in systemic candida infections? *Annals Pharmacother.* **30**:811–818 (1996).
2. G. G. Chabot, R. Pazdur, F. A. Valeriote, and L. H. Baker. Pharmacokinetics and toxicity of continuous infusion amphotericin B in cancer patients. *J. Pharm. Sci.* **78**:307–310 (1989).
3. J. R. Starke, E. O. Mason, Jr., W. G. Kramer and S. L. Kaplan. Pharmacokinetics of amphotericin B in infants and children. *J. Infect. Dis.* **155**:766–774 (1987).
4. G. Koren, A. Lau, J. Klein, C. Golas, M. Bologa-Campeanu, S. Soldin, S. M. MacLeod, and C. Prober. Pharmacokinetics and adverse effects of amphotericin B in infants and children. *J. Pediatr.* **113**:559–563 (1988).
5. A. J. Atkinson, Jr., and J. E. Bennett. Amphotericin B pharmacokinetics in humans. *Antimicrob. Agents Chemother.* **13**:271–276 (1978).
6. H. H. Chow, Y. Wu, and M. Mayersohn. Pharmacokinetics of amphotericin B in rats as a function of dose following constant-rate intravenous infusion. *Biopharm. Drug Disposit.* **16**:461–473 (1995).
7. L. H. Wang, R. M. Fielding, P. C. Smith, and L. S. S. Guo. Comparative tissue distribution and elimination of amphotericin B colloidal dispersion (Amphocil®) and Fungizone® after repeated dosing in rats. *Pharm. Res.* **12**:275–283 (1995).
8. H. H. Chow, Y. Cai, and M. Mayersohn. Disposition kinetics of amphotericin B in rats: the influence of dose. *Drug Metab. Dispos.* **20**:432–435 (1992).
9. R. M. Fielding, P. C. Smith, L. H. Wang, J. Porter, and L. S. S. Guo. Comparative pharmacokinetics of amphotericin B after administration of a novel colloidal delivery system, ABCD, and a conventional formulation to rats. *Antimicrob. Agents Chemother.* **35**:1208–1213 (1991).
10. K. Wasan, K. Vadiei, G. Lopez-Berestein, and D. R. Luke. Pharmacokinetics, tissue distribution and toxicity of free and liposomal amphotericin B in diabetic rats. *J. Infect. Dis.* **161**:562–566 (1990).
11. K. Vadiei, G. Lopez-Berestein, and D. R. Luke. Disposition and toxicity of amphotericin B in the hyperlipedimic zucker rat model. *Int. J. Obesity* **14**:465–472 (1990).
12. H. Kim, D. Loebenberg, A. Marco, S. Symchowicz, and C. Lin. Comparative pharmacokinetics of Sch 28191 and amphotericin B in mice, rats, dogs and cynomolgus monkeys. *Antimicrob. Agents Chemother.* **26**:446–449 (1984).
13. J. A. Gondal, R. P. Swartz, and A. Rahman. Therapeutic evaluation of free and liposome-encapsulated amphotericin B in the treatment of systemic candidiasis in mice. *Antimicrob. Agents Chemother.* **33**:1544–1548 (1989).
14. J. W. Lee, M. A. Amantea. P. A. Francis, E. E. Navarro, J. Bacher, P. A. Pizzo, and T. J. Walsh. Pharmacokinetics and safety of a unilammelar liposomal formulation of amphotericin B (ambisome) in rabbits. *Antimicrob. Agents Chemother.* **38**:713–718 (1994).
15. L. C. Edmonds, L. Davidson, and J. S. Bertino. Effect of variation in infusion time and macrophage blockade on organ uptake of amphotericin B-deoxycholate. *J. Antimicrob. Chemother.* **28**:919–924 (1991).
16. P. C. Craven, T. M. Ludden, D. J. Drutz, W. Rogers, K. A. Haegele, and H. B. Skrdlant. Excretion pathways of amphotericin B. *J. Infect. Dis.* **140**:329–341 (1979).
17. F. A. Jagdis, P. D. Hoeprich, R. M. Lawrence, and C. P. Schaffner. Comparative pharmacology of amphotericin B and amphotericin B methyl ester in the non-human primate, Macaca mulatta. *Antimicrob. Agents Chemother.* **12**:582–590 (1977).
18. A. Hutchaleelaha, H. H. Chow, and M. Mayersohn. Comparative pharmacokinetics and interspecies scaling of amphotericin B in several mammalian species. *J. Pharm. Pharmacol.* **49**:178–183 (1997).
19. E. R. Block, J. E. Bennett, L. G. Livoti, W. J. Klein, R. R. MacGregor, and L. Henderson. Fluocytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. *Ann. Intern. Med.* **80**:613–617 (1974).
20. W. L. Chiou, G. Robbie, S. M. Chung, T. C. Wu, and C. Ma. Relationship of plasma clearance of 54 extensively metabolized drugs between humans and rats: mean allometric coefficient of 0.66. *Pharm. Res.* (in press).
21. C. L. Golas, C. G. Prober, S. M. MacLeod, and S. J. Soldin. Measurement of amphotericin B in serum or plasma by high-performance liquid chromatography. *J. Chromatogr.* **278**:387–395, (1983).
22. W. L. Chiou. Critical evaluation of the potential error in pharmacokinetic studies of using linear trapezoidal rule method for calcula-

tion of the area under the plasma level-time curve. *J. Pharmacokin. Biopharm.* **6**:539–546 (1978).
23. W. L. Chiou, Compartment- and model-independent linear plateau principle of drugs during a constant-rate absorption or intravenous infusion. *J. Pharmacokinet. Biopharm.* **8**:311–318 (1980).
24. W. L. Chiou. New calculation method of mean total body clearance of drugs and its application to dosage regimens. *J. Pharm. Sci.* **69**:90–91 (1980).
25. W. L. Chiou. New calculation method for mean apparent drug volume of distribution and application to rational dosage regimens. *J. Pharm. Sci.* **68**:1067–1069 (1979).
26. H. Boxenbaum. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. *J. Pharmacokin. Biopharm.* **10**:201–227 (1982).
27. M. A. Gales and B. J. Gales. Rapid infusion of amphotericin B in dextrose. *Annals Pharmacother.* **29**:523–529 (1995).
28. D. D. Bindschadler and J. E. Bennett. A Pharmacologic guide to the clinical use of amphotericin B. *J. Infect. Dis.* **120**:427–436 (1969).
29. D. J. Morgan, M. S. Ching, K. Raymond, R. W. Bury, L. Mashford, B. Kong, J. Sabto, W. Gurr, and A. A. Somogyi Elimination of amphotericin B in impaired renal function. *Clin. Pharmacol. Ther.* **34**:248–253 (1983).
30. J. M. Benson and M. C. Nahata. Pharmacokinetics of amphotericin B in children. *Antimicrob. Agents Chemother.* **33**:1989–1993 (1989).
31. M. Bouley, M. Todd, P. Chavanet, and O. Petitjean. The penetration of amphotericin B from an intralipid formulation into fibrin loci in a rabbit model of candidiasis. *Biopharm. Drug Disposit.* **15**:485–492 (1994).
32. R. M. Fielding, A. W. Singer, L. H. Wang, S. Babbar, and L. S. S. Guo. Relationship of pharmacokinetics and drug distribution in tissue to increased safety of amphotericin B colloidal dispersion in dogs. *Antimicrob. Agents Chemother.* **36**:299–307 (1992).