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Comparative Pharmacokinetics and Interspecies Scaling of Amphotericin B in Several Mammalian Species

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Abstract

This study employed several interspecies scaling methods, to evaluate the applicability of extrapolating to man, pharmacokinetic information obtained from animals for amphotericin B, an anti-fungal drug.

Pharmacokinetic parameters from four animal species (mouse, rat, monkey and dog) and man were obtained from the literature or from analysis of data reported in the literature. The allometric relationships (obtained from four animal species) as a function of species body weight (W; kg) for systemic clearance per maximum life span potential (CL_S/MLP), steady-state volume of distribution (V_{SS}), apparent volume of distribution (V_β) and volume of the central compartment (V_C) were: $5691W^{1.096}$; $2.46W^{0.839}$; $3.08W^{0.948}$ and $1.07W^{0.965}$, respectively. The allometric relationships for half-life (h) and mean residence time (h) did not scale well with body weight. The prediction of pharmacokinetic parameters in man from the allometric equations do not always agree with those reported in the literature which are based upon a limited number of studies with few human subjects. The plasma concentration–time profiles from these animals were adjusted by normalizing the concentration with dose/$W^{0.948}$, and re-plotted on different pharmacokinetic time scales.

The syndesichrons plot produced an almost superimposable profile of adjusted concentrations as a function of adjusted time among the four species.

Since its discovery in 1953, amphotericin B has remained the drug of choice for the treatment of most disseminated fungal infections (Graybill & Craven 1983). Use of this drug has increased during the last decade as a result of a dramatic increase in patient populations with defective immune response. These patient groups include those with AIDS and cancer, and organ transplant patients who are more susceptible to life-threatening systemic fungal infection (Bronnimann et al 1987). As a result, at least in part, of the limited pharmacokinetic information about this agent, the current therapeutic dosage regimens of amphotericin B are complex (Jagdis et al 1977; Atkinson & Bennett 1978; Craven et al 1979; Arning & Scharf 1989). The decisions for selecting daily dose, total dose and duration of therapy are often governed by the prescribing physician's clinical experience in treating fungal infections as opposed to reliable dosing guidelines and therapeutic endpoints.

One of the major aims of interspecies scaling of pharmacokinetic parameters is to be able to predict disposition kinetics of drugs or toxicants in man on the basis of data from small laboratory animals. Allometric equations express the relationship for anatomical and physiological parameters as a function of body weight raised to a power:

$$Y = aW^b \quad (1)$$

where Y is the dependent physiological or anatomical parameter, W is the species body weight and a and b are the coefficient and exponent, respectively. Clearance and physiological flow-rate are often related to body weight with exponents of 0·75. Volumes of distribution relate to body weight with an exponent of approximately 1·0 (Mordenti & Chappell 1989).

The purpose of this study was to examine allometric relationships for the pharmacokinetic parameters of amphotericin B and to evaluate the possibility of extrapolating this information from animals to man.

Materials and Methods

The pharmacokinetics of amphotericin B have been reported for the mouse (Kim et al 1984), rat (Kim et al 1984; Vadiei et al 1990; Chow et al 1992), monkey (Jagdis et al 1977; Kim et al 1984), dog (Craven et al 1979; Kim et al 1984), and for man (Atkinson & Bennett 1978; Chabot et al 1989). In these studies amphotericin B was administered intravenously as a bolus dose (Kim et al 1984), as an infusion (Jagdis et al 1977; Craven et al 1979; Vadiei et al 1990; Chow et al 1992) and as chronic dosing regimens (Atkinson & Bennett 1978; Chabot et al 1989). The doses administered to animals were in the range 0·1 to 1·2 mg kg^{-1}; those to man were 70 mg day^{-1} and 70 mg every other day (Atkinson & Bennett 1978) and 1·01 to 3·68 mg kg^{-1} (Chabot et al 1989). In all species plasma amphotericin B concentrations were determined either by specific bioassay or by high-performance liquid chromatography. All plasma concentration–time data (with the exception of one set of data (Jagdis et al 1977)) were interpolated from graphs contained in these literature reports using a computer-based digitizer (Easydij, version 8·1, Geocomp, Golden, Colorado). We have assumed throughout our analyses that amphotericin B disposition might be described by linear processes (i.e. first-order kinetics).

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Values for total-body or systemic clearance (CL_S), steady-state volume of distribution (V_{SS}), apparent volume of distribution (V_β), volume of the central compartment (V_C), half-life ($t_{\frac{1}{2}}$) and mean residence time (MRT) for each species were obtained from the data reported in the literature or from an analysis of the data. The data were then further analysed by area/moment analysis using the Lagran program (Rocci & Jusko 1983). Both body weight and the pharmacokinetic parameters for amphotericin B in each species were transformed logarithmically and fitted to the equation:

$$\ln Y = \ln a + b \ln W \quad (2)$$

using linear least-squares regression analysis. The statistical significance of the correlation was assessed by testing the hypothesis that the slope of the regression line was equal to zero.

In order to compare the plasma concentration-time data from various species, biexponential disposition parameters were determined from the data (Boxenbaum & Ronfeld 1983). For non-bolus intravenous data, parameters were adjusted to those which would have been obtained had an intravenous bolus dose been administered. The concentration–time data were then normalized using several approaches developed by Boxenbaum and co-workers (Boxenbaum 1983, 1984; Boxenbaum & Ronfeld 1983). A complex Dedrick plot (apolysichrons) for the two-compartment model was obtained by plotting $C_t/(D/W^Y)$ against $W^{(X-Y)}$ on a semi-logarithmic scale (Boxenbaum & Ronfeld 1983); C_t is the concentration at different times after administration of amphotericin B, D is the administered dose and X and Y are the allometric exponents of clearance and volume of distribution, respectively. A simple biexponential equation ($Ae^{-\alpha t} + Be^{-\beta t}$) was used to fit the data using the SimuSolv program (1990). The coefficients and exponents that best described the equation were obtained.

The application of longevity concepts to the kinetic profiles of amphotericin B was achieved by linear least-squares regression fitting of the equation (Boxenbaum 1982):

$$CL_S \times MLP = kW^M \quad (3)$$

where MLP is maximum life span potential whose value for each species was obtained from the literature (Boxenbaum 1982). By incorporating this relationship and the allometric equation of volume of distribution into the biexponential equation, a dienetichrons plot can be obtained by plotting $C_t/(D/W^Y)$ against $W^{(X-Y)}t/MLP$ on a semi-logarithmic scale. The data were then fitted to a biexponential equation as described above. Applying the relationship between MLP and brain weight (BW) and body weight (W) (Sacher 1959) to equation 3, gave the relationship:

$$CL_S = nBW^Z W^X \quad (4)$$

A syndesichrons plot was constructed by plotting $C_t/(D/W^Y)$ against $BW^Z W^{(X-Y)}t$ on a semi-logarithmic scale. All data were fit to a biexponential equation as described above.

The Akaike information criterion (Akaike 1978) was used to compare the quality of curve fitting of the normalized concentrations as a function of the different pharmacokinetic times.

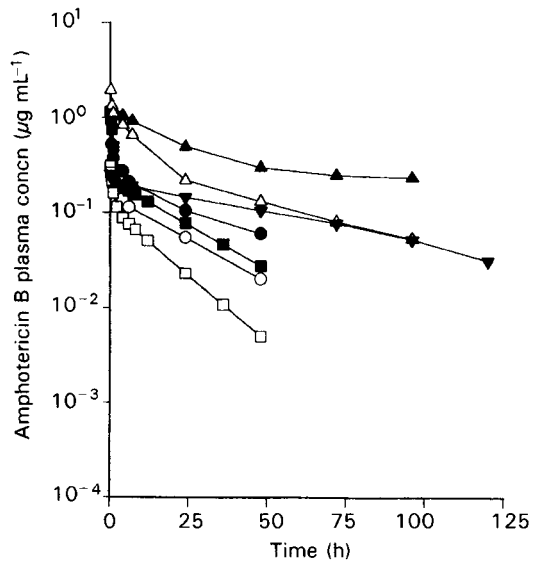

FIG. 1. Plasma concentration–time profiles (semi-logarithmic scale) of amphotericin B in several mammalian species. (●) Mice (0·6 mg kg^{-1}); (□) rats 1 (1·2 mg kg^{-1}); (■) rats 2 (0·45 mg kg^{-1}); (○) rats 3 (0·6 mg kg^{-1}); (▲) monkeys 1 (1 mg kg^{-1}); (△) monkeys 2 (0·6 mg kg^{-1}); (▽) dogs (0·6 mg kg^{-1}).

Results and Discussion

Fig. 1 illustrates amphotericin B plasma concentrations as a function of time in four different species after transformation of the data to biexponential disposition kinetic profiles assuming intravenous bolus administration. These profiles, not surprisingly, differ markedly among the several species for which data are available. Pharmacokinetic parameters reported and calculated for each species are summarized in Table 1.

The estimated allometric equations for pharmacokinetic parameters are shown in Table 2. Figs 2 and 3 show the allometric plots of these parameters as a function of body weight. Total body clearance scales to body weight with the exponent 0.747 (Fig. 2). In general, for compounds that are eliminated by more than one process, the allometric relationship for each process might have a different body weight exponent, and a poor correlation of the allometric relationship might be obtained for total body clearance (Hayton 1989). As for amphotericin B, the mechanisms responsible for its clearance from the body are not known and most data suggest the involvement of more than one process. Renal and biliary clearance of amphotericin B were found to account for 3–40% of systemic clearance depending on the species used in the investigation (Jagdis et al 1977; Atkinson & Bennett 1978; Craven et al 1979; Arning & Scharf 1989). Renal excretion of amphotericin B seems to be a relatively minor pathway for the elimination of amphotericin B in man, accounting for only 3·1% of total elimination. In the dog, total excretion of amphotericin B in urine accounted for 21% of the administered dose and 19% of the dose was recovered from the stool (Craven et al 1979). In rats, 10 to 25% of the dose was recovered in urine depending on the dose (Chow et al 1992). No metabolites of amphotericin B have yet been identified in in-vivo and in-vitro studies (Christiansen et al 1985), although the possible loss of amphotericin B through autooxidation has been suggested (Teraoka et al 1992). Despite these discrepancies among species in the clearance process, the allo-

Table 1. Pharmacokinetic parameters of amphotericin B from several mammalian species.

Species (reference)	Number of animals	Dose (mg)	Weight (kg)	Total body clearance ($mL\,min^{-1}$)	Steady-state volume of distribution (L)	Apparent volume of distribution (L)	Volume of the central compartment (L)	Half-life (h)	Mean residence time (h)
Mouse									
(Kim et al 1984)	4	0·011	0·019	0·02	0·06	0·06	0·02	27·5	37·0
Rat									
(Vadiei et al 1990)	6	0·240	0·200	0·59	0·83	0·89	0·19	16·0	25·5
(Chow et al 1992)	6	0·112	0·250	0·98	0·87	0·98	0·36	10·1	13·4
(Kim et al 1984)	4	0·135	0·225	0·66	1·01	0·95	0·35	17·3	23·5
Monkey									
(Jagdis et al 1977)	2	5·80	5·80	2·06	6·54	6·93	4·65	56·2	52·9
(Kim et al 1984)	3	3·00	5·00	2·18	6·39	7·14	1·98	35·3	41·5
Dog									
(Kim et al 1984)	5	6·90	11·5	8·29	31·5	31·5	27·2	41·3	63·2
(Craven et al 1979)	4	4·12	20·6	16·0	–	147	–	91·2	–
Man									
(Atkinson & Bennett 1978)									
Patient 217	1	70	65·4	24·0	243	187	26·3	336	169
Patient 220	1	70	74·2	36·1	317	263	35·4	396	146
(Chabot et al 1989)	14	71–258	–	11·7	224	–	–	264	288

Table 2. Allometric relationships for the pharmacokinetic parameters of amphotericin B across four species.

Parameter	Allometric equation	r^2	*P*-value
Total body clearance ($mL\,min^{-1}$)	$1{\cdot}19W^{0{\cdot}747}$	0·88	< 0·050
Total body clearance × maximum life span potential (L/maximum life span potential)	$5691W^{1{\cdot}096}$	0·97	< 0·001
Steady-state volume of distribution (L)	$2{\cdot}46W^{0{\cdot}839}$	0·96	< 0·001
Apparent volume of distribution (L)	$3{\cdot}08W^{0{\cdot}948}$	0·95	< 0·050
Volume of the central compartment (L)	$1{\cdot}07W^{0{\cdot}965}$	0·94	< 0·001
Half-life (h)	$26{\cdot}69W^{0{\cdot}162}$	0·39	0·121
Mean residence time (h)	$34{\cdot}58W^{0{\cdot}136}$	0·36	0·144

metric relationship of CL_S across these species has a relatively high correlation ($r^2 = 0{\cdot}88$).

The systemic clearance of amphotericin B, however, can be characterized as being restrictive (low clearance or small extraction ratio) in all species. On the basis of the well-stirred model, the clearance of a restrictively cleared drug is approximately equal to the fraction unbound in plasma (f_U) multiplied by the unbound intrinsic clearance ($CL_{U,I}$). The allometric relationship for clearance will, therefore, be dependent upon the allometric relationships for both f_U and $CL_{U,I}$; values for these parameters are, unfortunately, not available. It seems, however, that f_U does not scale with weight across species (McNamara 1991).

Another approach to improving the correlation of allometric relationships for clearance is to consider that animals with longer life spans tend to have lower clearance values. This approach improves interspecies scaling for the clearance of many compounds such as antipyrine, phenytoin and clonazepam (Boxenbaum 1982). When scaling CL_S per MLP as a function of body weight, a better allometric correlation is obtained among all the species ($r^2 = 0{\cdot}97$, $P < 0{\cdot}001$) and the exponent of body weight was 1·096 (Fig. 2).

Interspecies scaling with body weight of steady-state volume of distribution, apparent volume of distribution and volume of the central compartment showed good correlations, with r^2 values of 0·96, 0·95 and 0·94, respectively (Fig. 2). The allometric exponents of the three volumes were 0·839, 0·948 and 0·965, respectively, indicating that the apparent volume of distribution and the central volume of distribution are nearly a constant fraction of the body weight in all species.

Half-life and mean residence time did not scale well with body weight ($r^2 = 0{\cdot}39$ and 0·36, respectively; Fig. 3). The allometric exponents of half-life and mean residence time were 0·162 and 0·136, respectively. Theoretically, these allometric exponents should be equal to the difference between the exponents for volume of distribution and clearance (0·201 and 0·092 for half-life and mean residence time, respectively).

Plasma concentrations of amphotericin B tend to decline more rapidly with chronological time in small animals than in larger animals (Fig. 1). This is, in part, because small animals have larger elimination organs in proportion to their body size. There are several methods for adjusting data based on chronological time into pharmacokinetic time which eliminates this source of variance among species (Boxenbaum 1983, 1984; Boxenbaum & Ronfeld 1983). The so called complex Dedrick plot uses exponents from the allometric equations of clearance and volume of distribution to convert chronological time into pharmacokinetic time. For amphotericin B, whose plasma concentration-time profile was assumed to be biexponential,

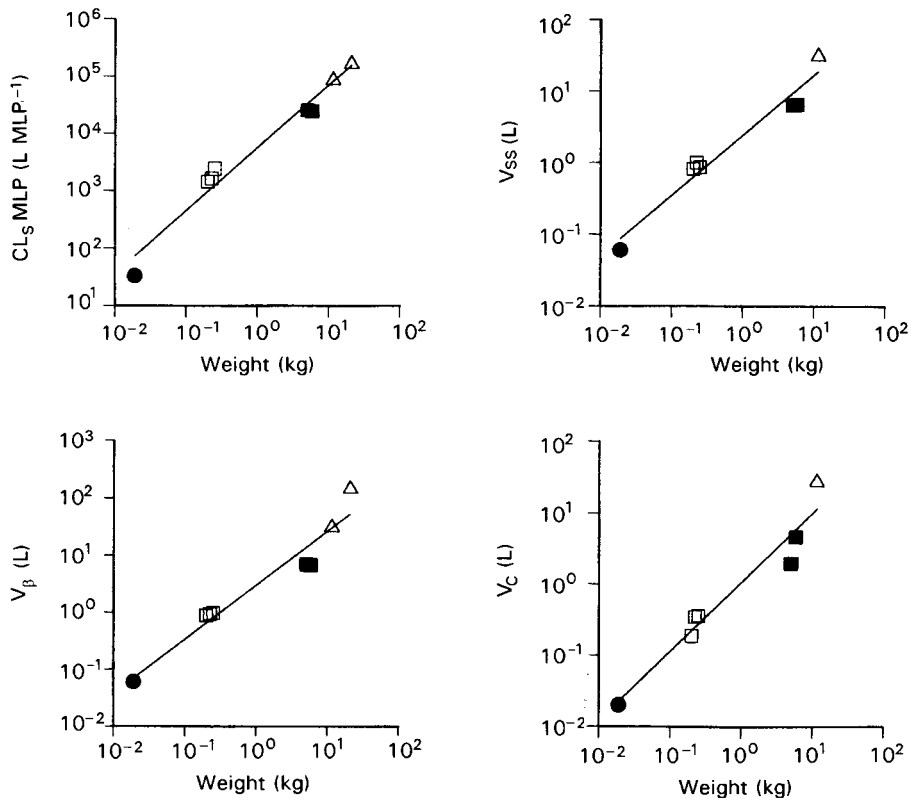

FIG. 2. Log-log plots of clearance per MLP, steady-state volume of distribution (V_{SS}), apparent volume of distribution (V_β) and volume of the central compartment (V_C) against species body weight. The solid lines represent linear regression analysis of the data. Equation of the lines are presented in Table 2. (●) mice, (□) rats, (■) monkeys, (△) dogs.

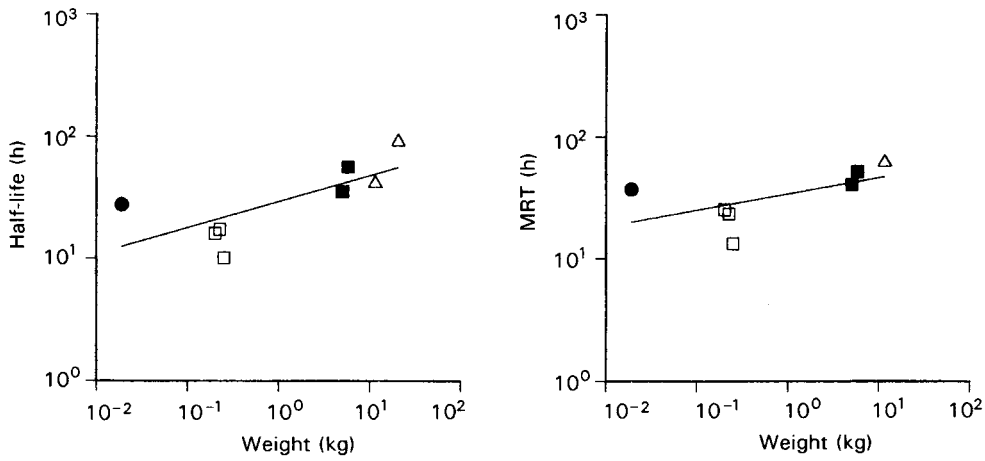

FIG. 3. Log-log plots of half-life and mean residence time (MRT) against species body weight. Equations of the lines are presented in Table 2. (●) mice, (□) rats, (■) monkeys, (△) dogs.

and by assuming that all volume terms have the same exponent (0·948), the semi-logarithmic plot between $C_t/(D/W^{0.948})$ and $W^{0.201}t$ (apolysichrons) helps to improve fitting to some extent (Fig. 4).

Boxenbaum (1982) has included MLP to adjust for species differences in unbound intrinsic clearance of antipyrine, phenytoin and clonazepam and he found a good linear relationship with body weight across several species. By incorporating MLP into the allometric relationship to normalize chronological time the transformed concentration-time profiles were superimposable (Boxenbaum 1983). For amphotericin B, the log-log plot of CL_S per MLP against body weight showed a good linear correlation (Fig. 2). The semi-logarithmic plot of $C_t/(D/W^{0.948})$ and $W^{0.148}t$/MLP (dienetichrons), assuming that

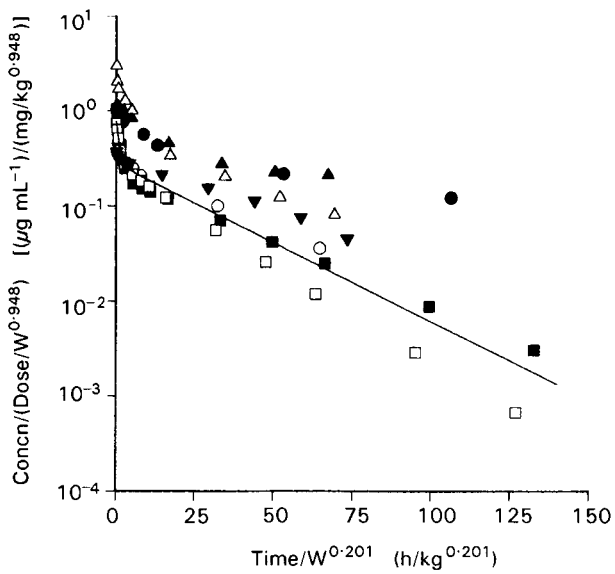

FIG. 4. Complex Dedrick plot (apolysichrons) of amphotericin B plasma concentration-time data from several species based upon the data illustrated in Fig. 1. The solid line represents a non-linear regression analysis of the data assuming a biexponential equation. The equation of the line is presented in Table 3. (●) mice (0·6 mg kg^{-1}); (□) rats 1 (1·2 mg kg^{-1}); (■) rats 2 (0·45 mg kg^{-1}); (○) rats 3 (0·6 mg kg^{-1}); (▲) monkeys 1 (1 mg kg^{-1}); (△) monkeys 2 (0·6 mg kg^{-1}); (▽) dogs (0·6 mg kg^{-1}).

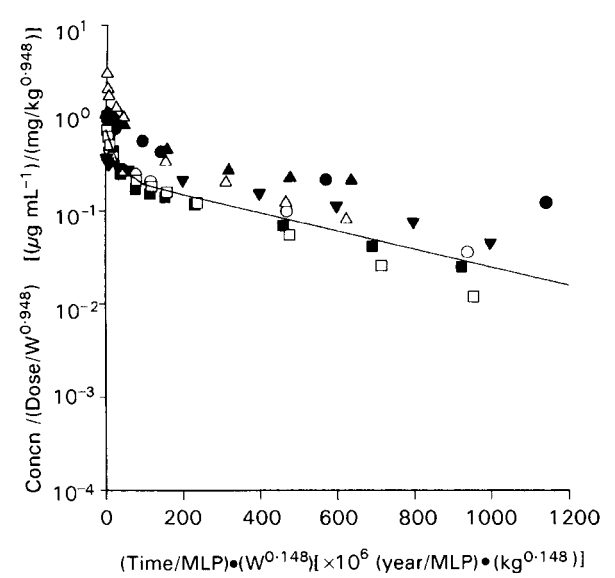

FIG. 5. Dienetichron plot of amphotericin B plasma concentration-time data from several species based upon the data illustrated in Fig. 1. The solid line represents a non-linear regression analysis of the data assuming a biexponential equation. The equation of the line is presented in Table 3. (●) mice (0·6 mg kg^{-1}); (□) rats 1 (1·2 mg kg^{-1}); (■) rats 2 (0·45 mg kg^{-1}); (○) rats 3 (0·6 mg kg^{-1}); (▲) monkeys 1 (1 mg kg^{-1}); (△) monkeys 2 (0·6 mg kg^{-1}); (▽) dogs (0·6 mg kg^{-1}).

all volume terms have the same exponent (0·948), produced a better fit to the data among the four species in comparison with the complex Dedrick plot (Fig. 5).

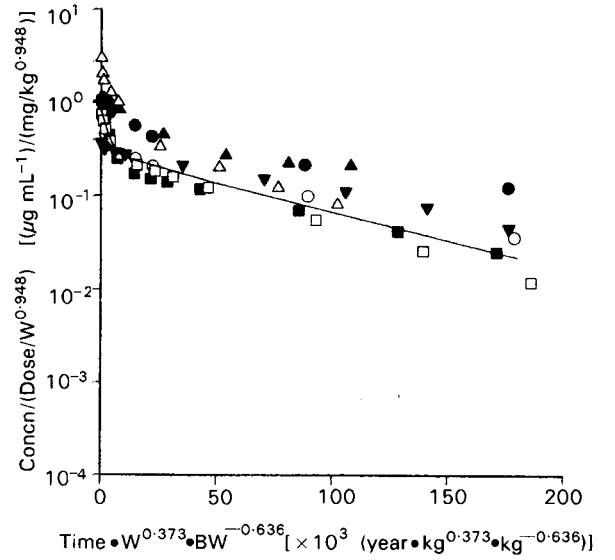

FIG. 6. Syndesichron plot of amphotericin B plasma concentration-time data from several species based upon the data illustrated in Fig. 1. The solid line represents a non-linear regression analysis of the data assuming a biexponential equation. The equation of the line is presented in Table 3. (●) mice (0·6 mg kg^{-1}); (□) rats 1 (1·2 mg kg^{-1}); (■) rats 2 (0·45 mg kg^{-1}); (○) rats 3 (0·6 mg kg^{-1}); (▲) monkeys 1 (1 mg kg^{-1}); (△) monkeys 2 (0·6 mg kg^{-1}); (▽) dogs (0·6 mg kg^{-1}).

The syndesichron plot (Boxenbaum 1984) was obtained by incorporating a relationship between MLP and brain weight and body weight into the relationship of CL_S per MLP. This approach enables more flexibility in correcting clearance because the relationship has two power terms. Owing to the limited amount of amphotericin B data, we were unable to obtain good estimates for the coefficient and exponent of equation 4. We therefore substituted the defined relationship between MLP (years) and brain weight (kg) and body weight (kg) (i.e., $MLP=185{\cdot}4BW^{0{\cdot}636}W^{-0{\cdot}225}$; Sacher 1959) into equation 3 to obtain equation 4. The semi-logarithmic plot of $C_t/(D/W^{0{\cdot}948})$ against $BW^{-0{\cdot}636}W^{0{\cdot}373}t$ (syndesichrons), assuming all volume terms have the same exponent (0·948), produces a nearly superimposable profile among the four species (Fig. 6).

Table 3 lists the parameters of the biexponential equations that best described the normalized concentration-time profiles from the three plotting methods. The Akaike information criteria for the apolysichron, dienetichron and syndesichron plots were 221·5, 163·2 and 155·2, respectively. These results suggest that the transformed amphotericin B concentration-time data based upon syndesichrons minimizes biological variance among these species. It should be recognized, however, that the additional parameter in this relationship (brain weight, BW) would be expected to improve the quality of the fit to the data compared with a relationship with fewer parameters.

When attempting to predict clearance and volume of distribution in man on the basis of allometric equations from four animal species, the values obtained do not always agree with those reported in the literature (Atkinson & Bennett 1978; Chabot et al 1989) (Table 4). The reasons for these discrepancies are not clear. The pharmacokinetic parameters of

Table 3. The parameters of a biexponential equation describing different normalized amphotericin B concentrationtime plots.

Pharmacokinetic time	A ($kg^{0.948} mL^{-1}$)	B ($kg^{0.948} mL^{-1}$)	α	β	Akaike information criterion
Apolysichrons	0·285	0·087	0·0560	0·0371	221·5
Dienetichrons	0·517	0·234	45384	2241	163·2
Syndesichrons	0·571	0·273	338·59	14·00	155·2

Table 4. Comparison of predicted pharmacokinetic parameters of amphotericin B in man with literature values obtained from patient populations.

Source of data	Total body clearance ($mL\,min^{-1}$)	Steady-state volume of distribution (L)	Half-life (h)	Mean residence time (h)
This work	8·6	87	109	98
Atkinson et al (1978)	30·1	279	360	155
Chabot et al (1989)	11·7	224	264	288

amphotericin B in man were obtained after long-term treatment of patients with numerous and different underlying diseases and in ill patients receiving other drugs. Further, the predicted parameters for man might better represent values in healthy subjects after receiving a single dose of amphotericin B; this issue needs further investigation, however.

Although the disposition processes of amphotericin B tend to be different among the species and the data obtained in the literature have inherent variations among laboratories, reasonably good allometric relationships of pharmacokinetic parameters of amphotericin B across several mammalian species were obtained.

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