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Population Pharmacokinetics and Renal Function-Sparing Effects of Amphotericin B Colloidal Dispersion in Patients Receiving Bone Marrow Transplants

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The purpose of this study was to evaluate the pharmacokinetics of amphotericin B colloidal dispersion and its effect on creatinine clearance in bone marrow transplant patients with systemic fungal infections. Seventy-five patients (42 females and 33 males) with a median age of 34.5 years and a median weight of 70.0 kg were enrolled in the study. Patients received 1 of 15 dose levels (range, 0.5 to 8.0 mg/kg of body weight) daily for a mean duration of 28 days and a mean cumulative dose amount of 8 g. Plasma samples for amphotericin B determination (median number, 4; range, 2 to 30) and daily serum creatinine values were obtained for each patient. Iterative two-stage analysis, one of several approaches to population pharmacokinetic and pharmacodynamic modelling, was employed for the pharmacokinetic analysis. The plasma data were available for 51 of 75 patients and were best described by a two-compartment model. Both plasma clearance and volume of distribution increased with escalating doses; the overall average terminal elimination half-life was 29 h. Of the covariates studied, only body weight and dose size were significant. Serum creatinine values over the duration of therapy were available for 59 of 75 patients. Overall, there was no net change in renal function over the duration of therapy; 12 patients had >30% increases in creatinine clearance, whereas 13 had >30% decreases. No measure of amphotericin B colloidal dispersion exposure, demographic values, or concomitant treatment with other medications was related to changes in the creatinine clearance.

Patients undergoing bone marrow transplant procedures receive a plethora of immunosuppressive agents. These patients are vulnerable to infections with a number of opportunistic organisms, including fungi. In a recent review of over 1,500 patients undergoing bone marrow transplants, the incidence of invasive candidiasis was 11% and that of invasive aspergillosis was 4.5%, with mortalities of 73 and 84%, respectively (22).

Amphotericin B (AmB), a polyene antibiotic that is available as a deoxycholate micellar dispersion (DAmB), has been the mainstay of systemic antifungal therapy for almost 4 decades. Its antifungal activity is due to its affinity for sterols (ergosterols) found in the membranes of fungal cells. However, its undesirable binding to host cell sterols is believed to account for its various toxicities, which include nausea, vomiting, chills, fever, anemia, and thrombophlebitis (14, 21, 27). The primary dose-limiting toxicity of AmB is nephrotoxicity, which occurs in up to 80% of patients receiving cumulative doses of 4 to 5 g. Consequently, the cumulative amount of AmB that can be administered to patients and the duration of treatment are limited (12, 15). The potential for nephrotoxicity poses a therapeutic challenge for bone marrow transplant recipients, for whom long-term therapy with DAmB for the treatment of systemic suspected or documented fungal disease is generally required. Furthermore, many of these patients are receiving other nephrotoxic drugs such as cyclosporine, FK-506, aminoglycoside antibiotics, and vancomycin, some of which have synergistic nephrotoxic effects when coadministered with DAmB (28).

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Recently, lipid-based formulations of AmB have been developed in an attempt to attenuate the toxicities associated with AmB, to potentially target active sites of infection, and to improve the therapeutic ratio of the drug (18–20, 30). One such product is a colloidal suspension of AmB, amphotericin B colloidal dispersion for injection (ABCD). ABCD is a lipid complex of a near 1:1 molar ratio of AmB and sodium cholesteryl sulfate. The lipid complex suspension contains uniform discs approximately 115 nm in diameter and 4 nm in thickness (13).

In a phase I study, the single-dose (0.5 to 1.5 mg/kg of body weight) pharmacokinetics of ABCD were studied in healthy volunteers (26). There are no published data regarding the multiple-dose pharmacokinetics of ABCD in patients. This paper will describe the pharmacokinetics of ABCD administered daily to patients undergoing bone marrow transplantation. In addition, factors associated with changes in creatinine clearance (CL_{CR}) are explored.

MATERIALS AND METHODS

Patient selection. This was an open-label, single-center, dose escalation study designed to assess the safety and pharmacokinetics of ABCD for patients who were undergoing autologous or allogenic bone marrow transplantation and who had a variety of fungal infections, including documented candidiasis and aspergillosis and infections with *Torulopsis glabrata* or other molds. Apart from ABCD no systemic antifungal agents, other than prior therapy with DAmB, were permitted. In addition, patients who received other medications associated with bone marrow transplant protocols (e.g., cyclosporine, colony-stimulating factors, gentamicin, acyclovir) were included in the study. Patients with known sensitivities to DAmB, oncologic relapses, estimated creatinine clearances of <25 ml/min, liver enzymes at or above six times the normal level, or severe veno-occlusive disease were excluded.

Dose administration. Cohorts of three to seven patients were given daily ABCD doses that were escalated, between cohorts, by 0.5 mg/kg/day. The doses

TABLE 1. Summary of doses, durations, and samples obtained for 51 patients included in the pharmacokinetic analysis

Daily dose (mg/kg)	No. of patients	Median duration of therapy (days)	Median no. of samples
0.5	3	57	5
1.0	6	22	5
1.5	5	24	4
2.0	1	13	3
2.5	1	108	27
3.0	3	31	9
4.0	3	45	9
4.5	5	29	5
5.0	6	37	6
5.5	2	29	4
6.0	2	42	2
6.5	1	42	4
7.0	3	42	2
7.5	9	39	3
8.0	1	43	4

ranged from 0.5 to 8.0 mg/kg/day, and the daily dose amount for each patient was constant throughout the duration of therapy. Patients each received a 1.0-mg test dose of ABCD prior to initiation of their therapeutic doses. All subsequent doses were administered once daily by an intravenous zero-order infusion, at a rate of 1.0 mg/kg/h.

ABCD was supplied by SEQUUS Pharmaceuticals, Inc., in glass vials containing a sterile, nonpyrogenic, lyophilized cake of 100 mg of AmB. The lyophilized drug was reconstituted with 20.0 ml of sterile water for injection (USP) and diluted for injection with 5% dextrose to a final concentration of 0.625 mg of AmB per ml. Depending on the dose, the infusion volume ranged from approximately 50 to 800 ml.

Plasma sampling and analytical assay. Blood samples were generally obtained just prior to and at the end of an infusion of ABCD after one or more doses, while some patients had additional samples obtained at either 2 and 7 h or 1, 2, 6, 8, and 24 h. A median of 4 blood samples per patient (range, 2 to 30) was obtained.

The blood samples were collected into EDTA-containing tubes and centrifuged at 1,000 × *g* for 10 min, and the plasma fraction was removed and stored at −20°C for later determination of AmB concentrations. Total AmB concentrations in plasma were quantitated by a sensitive and specific high-performance liquid chromatography assay with UV detection by Bio-Research Laboratories LTD (Montreal, Canada). Solid-phase extraction was employed for sample preparation and extraction of AmB. The sensitivity of the assay was 10.0 μg/liter, and the linear range was 10.0 to 2,000 μg/liter. At 30 μg/liter, the precision was 8.1% and the accuracy was within 6% of the nominal value, whereas at 2,000 μg/liter, the values were 2.1 and 0.5%, respectively.

Pharmacometric methods of analyses. Patients were excluded from pharmacokinetic analyses if they had received prior doses of DAmB (within one week of ABCD therapy) and had plasma samples obtained only within the first 2 weeks of ABCD therapy. This restriction was applied to ensure that any contributions of prior DAmB to the concentrations in plasma would have decreased to negligible values, thus minimizing their effects upon the multiple-dose pharmacokinetics of ABCD.

The plasma AmB concentration data were characterized by fitting pharmacokinetic models to the data by iterative two-stage (IT2S) analysis (10, 11, 24, 25, 31), one of several approaches to mixed-effect modelling (also called population modelling) (25, 29, 31). The population pharmacokinetic values were determined by IT2S, a program which was developed with modules from the program package ADAPT II (5, 6). Briefly, the IT2S approach fits each of the individuals' data by a maximum a posteriori probability Bayesian estimator. The IT2S program combines the results of all the individual patients into a refined estimate of the pharmacokinetic parameters of the population model. These refined estimates are then used to update the maximum a posteriori probability estimator and then another fit (iteration) of the individual data sets is performed. This process continues until convergence is achieved. The initial estimates of the pharmacokinetic parameters were obtained from a single-dose study with human volunteers (26). Convergence of the IT2S analysis is considered to have occurred when the average maximum likelihood is stable (shows no net change in the fourth significant digit) for at least 10 iterations.

In this analysis, candidate structural population models and a model for the residual variance of the observations (i.e., the concentrations in plasma) were fitted to the experimental data. In addition, individual estimates for each subject (pharmacokinetic parameter point estimates and asymptotic covariance matrices) were generated during the process. Model discrimination was accomplished by the rule of parsimony (16) and Akaikes's information criterion (AIC) (1).

After the structural model was identified, both multiple linear regression with backward stepping and examination of scatter plots of the individual fitted pharmacokinetic parameters versus selected variables were utilized to identify potential covariates. Covariates, which either were significantly related by multiple linear regression ($\alpha < 0.05$) or appeared related to the pharmacokinetic parameters by observation of the scatter plots, were tested in the population model for improvement in AIC. The following covariates were evaluated: age, weight, height, body surface area, gender, baseline CL_{CR}, and bone marrow transplant type.

The empiric variance model for plasma AmB concentrations assumed that the residual (error) standard deviations (σ) of the observations were linearly related to the true values (Y) by the equation $\sigma = \nu_1 \cdot Y + \nu_2$, in which ν_1 and ν_2 are the variance parameters. The initial estimates for the variance parameters were chosen on the basis of the performance specifications for the analytical assay; later in the process, the values for the variance parameters were fitted (determined from the data).

The maximum AmB concentrations after the first dose and at steady state were obtained by simulations of the fitted pharmacokinetic parameters and dosage regimens for each patient. The 24-h area under the curve at steady state (AUC_{ss}) was calculated for each patient by dividing the daily dose by the fitted clearance.

Summary statistics are reported as the means and variances for the fitted population parameters. The derived pharmacokinetic values—volume of distribution at steady state (V_{ss}; the sum of the volumes of the central [V_1] and peripheral [V_p] compartments), AUC_{ss}, and the half-lives ($t_{1/2}$) of the initial [λ_1] and terminal [λ_2] phases—for the population are reported as the means, medians, minimum and maximum values, and coefficients of determination.

Assessment of renal function. To allow the manifestation of potential renal changes, patients were included in the renal-function analysis only if their durations of ABCD therapy were greater than 1 week. Daily serum creatinine values were obtained throughout the duration of ABCD treatment for each patient. The normalized (to 70 kg) CL_{CR}s were predicted daily by an equation that allowed for changing serum creatinine (4, 36). The median weekly CL_{CR}s during the first (CL_{CR1}) and last (CL_{CR2}) weeks of ABCD therapy were determined and compared statistically by the Wilcoxon signed rank test. Specific covariates such as dose, cumulative amount of ABCD, duration of therapy, and agents (e.g., cyclosporine, gentamicin, prior amphotericin B use) known to influence renal function were studied for their influences upon the percent change in CL_{CR} (percent change = $100 \cdot (CL_{CR2} - CL_{CR1})/CL_{CR1}$) by multiple linear regression with backward stepping. All statistical tests were considered significant at an α of 0.05, and changes in CL_{CR} of >30% were considered clinically significant. The computer package Systat for Windows, version 5.0, was used for all statistical computations (33).

RESULTS

Final pharmacokinetic model for ABCD. The 75 marrow transplant patients (42 females and 33 males) enrolled in the study had a median age of 34.5 (range, 3 to 58) years and a median weight of 70.0 (14 to 116) kg. The majority of the patients underwent transplantation for hematological malignancies. Of the patients, 62 received allogenic transplants and 13 received autologous transplants.

A total of 51 patients (29 females and 22 males) with a median age of 32.0 (range, 3 to 52) years and a median weight of 69.5 (13.7 to 116) kg were included in the pharmacokinetic analyses. Of these, 10 patients had not received prior conventional AmB therapy. The 24 patients excluded from the analyses had received prior treatment with conventional AmB and did not have plasma samples drawn beyond 2 weeks of ABCD therapy. A description of the number of patients included in the pharmacokinetic analyses by dose group, duration of therapy, and number of plasma samples obtained is shown in Table 1.

Plasma AmB concentrations were best fit by an open, two-

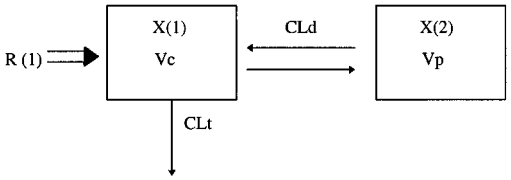

FIG. 1. Structural pharmacokinetic model. V_c, V_1. See text for definitions of other abbreviations.

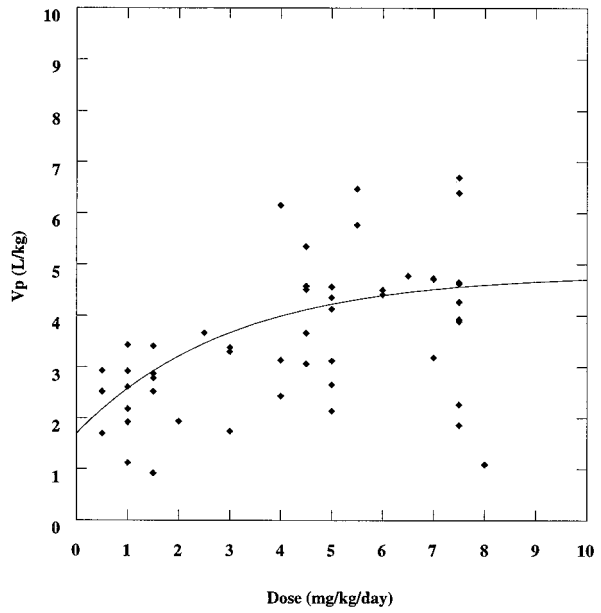

FIG. 2. Plot of individual values for V_p versus dose.

compartment structural model, with the intravenous infusion described by a zero-order process, R(1). The fitted pharmacokinetic model parameters included volumes of the central (V_1) and peripheral (V_p) compartments and distributional (CL_d) and total (CL_t) clearances. A scatter plot of the initial results of the individual fitted pharmacokinetic values indicated that the likelihood distribution for CL_d was right-skewed. Consequently, this parameter was modelled as a log normal distribution. Both CL_d and CL_t were modelled as linear processes. This model and its output (plasma concentrations) may be defined by the following ordinary differential and model output equations: (i) $XP(1) = R(1) - CL_d[X(1)/V_1 - X(2)/V_p] - X(1)/V_1 \cdot CL_t$, (ii) $XP(2) = CL_d[X(1)/V_1 - X(2)/V_p]$, and (iii) $Y(1) = X(1)/V_1$, where XP(1) and XP(2) represent the central and peripheral compartments, respectively, X(1) and X(2) are the amounts of drug in the central and peripheral compartments, respectively, and Y(1) is the fitted plasma concentration. Figure 1 depicts the structural pharmacokinetic model.

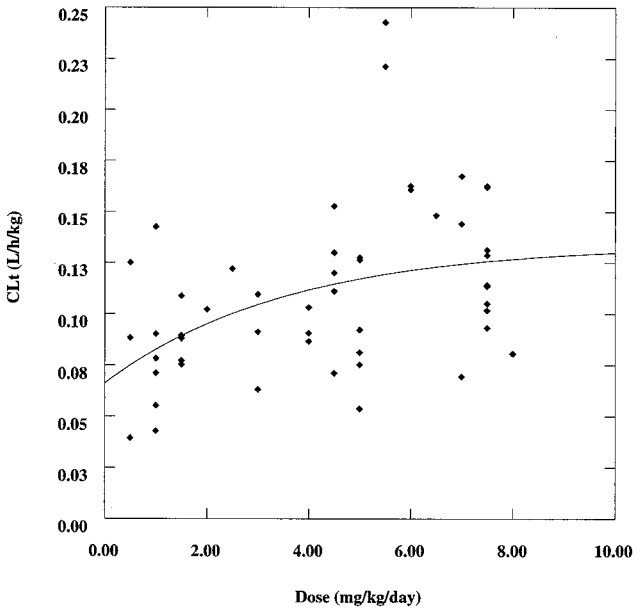

FIG. 3. Plot of individual values for CL_t versus dose. The smooth line is the fitted population mean.

TABLE 2. Fitted population pharmacokinetic parameter values for ABCD (see text for definitions)

Parameter (unit)	Mean	Variance
V_1 (liters/kg)	0.0894	0.00461
V_{po} (liters/kg)	1.69	1.51
V_{pmax} (liters/kg)	4.81	6.67
K_v ($dose^{-1}$)	0.334	0.0525
CL_d (liters/h/kg)	0.943	0.666
CL_{to} (liters/h/kg)	0.0661	0.00262
CL_{tmax} (liters/h/kg)	0.134	0.00351
K_{cl} ($dose^{-1}$)	0.278	0.0621

Of the covariates tested, only dose (in milligrams per kilogram) and body weight were identified by multiple linear regression and observation of the scatter plots to be related to both V_p (in liters per kilogram) and CL_t (in liters per hour per kilogram). Including these covariates in the model significantly decreased the AIC value from 3,200 (simple model) to 2,712 (model including weight and dose). Figures 2 and 3 display the individual estimates for V_p and CL_t, respectively, versus doses. The smooth lines through the individual points are the population mean values fitted by the following functions: (i) $V_p = V_{po} + (V_{pmax} - V_{po})[1 - \exp^{(-K_v \cdot dose)}]$ and (ii) $CL_t = CL_{to} + (CL_{tmax} - CL_{to})[1 - \exp^{(-K_{cl} \cdot dose)}]$. The asymptotic minima (V_{po} and CL_{to}) and maxima (V_{pmax} and CL_{tmax}) for V_p and CL_t and the coefficients of change (K_v and K_{cl}) for volume of distribution and clearance were fit for both V_p and CL_t (Table 2). The $\lambda_1 t_{1/2}$ and $\lambda_2 t_{1/2}$ phases were derived from the fitted parameters and are summarized for the population in Table 3. No change in the $\lambda_2 t_{1/2}$ was seen with increasing doses.

The model fit the observed data very well. This is evident in Figure 4, which shows the observed (Y) and fitted (X) plasma AmB concentrations for the 51 patients. The line of best fit through these data ($Y = 0.992 \cdot X + 0.951 \cdot 10^{-4}$) did not differ from the line of identity (reflecting a lack of bias), and the coefficient of determination was 0.954 (reflecting good precision). Linear regression of weighted residual (Y) versus fitted plasma concentrations [X(1)] and versus time [X(2)] likewise showed no bias. Neither slope ($P > 0.334$) nor intercept ($P > 0.223$) for either plot differed from zero [$Y = (3.5 \cdot 10^{-5})X(1) - 0.0876$; $Y = (9.4 \cdot 10^{-5})X(2) - 0.106$]. The

TABLE 3. Summary statistics for derived ABCD pharmacokinetic parameters[a]

Statistical index	Value for parameter			
	$\lambda_1 t_{1/2}$ (min)	$\lambda_2 t_{1/2}$ (h)	AUC_{ss} (μg/ml · h)	V_{ss} (liters/kg)
Minimum	0.213	10.8	4.12	1.02
Maximum	25.8	49.5	25.3	6.81
Median	3.78	28.4	9.69	3.45
Mean	6.6	29.0	10.5	3.61
CV (%)	103	31.3	40.7	39.7

[a] $n = 51$. AUC_{ss} is normalized to a 1-mg/kg/day dose of ABCD. CV, coefficient of variation, calculated as standard deviation/mean × 100.

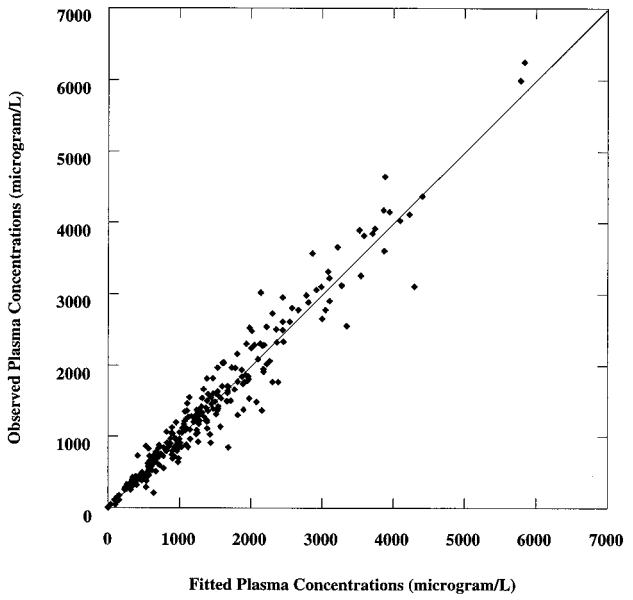

FIG. 4. Plot of observed versus fitted values for plasma AmB concentrations (51 patients, 300 plasma samples, $r^2 = 0.954$). The diagonal line is the line of identity.

fitted variance model ($\nu_1 = 0.1541$ and $\nu_2 = 10.0$ μg/liter) is also reflective of good precision.

A patient receiving 4.0 mg of ABCD per kg would have the following a priori pharmacokinetic values: V_1, 0.0894 liter/kg; V_p, 3.99 liters/kg; V_{ss}, 4.08 liters/kg ($V_{ss} = V_c + V_p$); CL_d, 0.597 liter/h/kg; CL_t, 0.112 liter/h/kg; $\lambda_1\ t_{1/2}$, 5.16 min; $\lambda_2\ t_{1/2}$, 29.8 h; maximum plasma drug concentration at steady-state, 2,800 μg/liter. Figure 5 depicts the predicted concentration-versus-time profile of AmB following a 4.0-mg/kg dose of ABCD administered daily for 10 days and infused over 4 h.

Five children less than 13 years of age were enrolled in this study in the 7.0- and 7.5-mg/kg/day dose levels. Although the number of children was limited, the comparison of estimates of pharmacokinetic parameters for children and adults in the same dose level groups suggests that ABCD has similar pharmacokinetics in children and adults (Table 4).

Of the 75 patients, 59 received at least eight days of ABCD therapy and were evaluated for changing renal function. Of these, the number of patients receiving other potentially nephrotoxic drugs were as follows: 9 received only prior DAmB, 3 received only cyclosporine, 29 received DAmB plus cyclosporine, 3 received DAmB plus gentamicin, 2 received cyclosporine plus gentamicin, and 13 received DAmB plus cyclosporine plus gentamicin. Of the 59 patients studied, 46 were also included in the pharmacokinetic analyses. The median values for duration of therapy and cumulative amount of ABCD received were 34 days (range, 8 to 108) and 8.44 g (range, 0.815 to 34.2), respectively. Overall, there was no significant change in CL_{CR} between the first (X) and last (Y) week of ABCD therapy ($P = 0.169$) (Fig. 6). The overall mean percent change in CL_{CR} for the 59 patients was −0.176% (range, −71.6 to 94.3%). Twelve patients had an increase in CL_{CR} of greater than 30%, whereas 13 had a decrease greater than 30%. None of the following variables were related to the percent change in CL_{CR} over the duration of therapy: ABCD daily dose (in milligrams per kilogram), cumulative amount of ABCD administered, number of days of therapy, bone marrow transplant type, sex, age, and administration or cumulative amounts of prior DAmB, cyclosporine, or gentamicin. Further, for the 46 patients included in the pharmacokinetic analyses, no measure of ABCD exposure (e.g., AUC_{ss} or average or maximum concentration) correlated with percent change in CL_{CR}. There was also no mean net change from baseline values in any hepatic function test (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or bilirubin) over the duration of ABCD therapy.

DISCUSSION

ABCD at 0.5 to 8.0 mg/kg/day displayed pharmacokinetics best described by an open, two-compartment structural model, with an initial decline reflecting distribution to rapidly equilibrating tissues followed by a prolonged terminal phase. Body weight and dose group accounted for a substantial portion of the variability of the pharmacokinetic estimates between patients. The increases in both V_p and CL_t with increasing doses suggest a possible saturable binding site within the central volume compartment.

The trend towards an increase in V_p with escalating doses of ABCD has also been reported in a single-dose pharmacokinetic study, in which ABCD was administered to healthy volunteers at doses of 0.25 to 1.5 mg/kg at an infusion rate of 0.5 mg/kg/h (26). The increase in plasma clearance with escalating doses is characteristic of drugs which display a restrictive clearance, that is, a clearance dependent on the amount of unbound drug. As the doses increase, binding sites within the central compartment may become saturated, resulting in a larger amount of drug becoming available for elimination from the plasma. However, in the single-dose escalation study (dose range, 0.5 to 1.5 mg/kg), the plasma clearance remained constant at a value of approximately 0.025 liter/h/kg, with a terminal $t_{1/2}$ of approximately 10 days (26). Since the highest dose of ABCD administered was 1.5 mg/kg, it is uncertain whether higher doses would have resulted in a similar increase in clearance. Curiously, at equivalent doses clearance was threefold larger after multiple dosing compared with the clearance from the single-dose study. This could be explained by study population differences, although there is preclinical evidence that the pharmacokinetics of ABCD may differ after multiple dosing. In a study of ABCD with dogs, a clearance that was larger than expected was also observed after multiple dosing (8). Since liposomal and colloidal particles are believed to be taken up by the reticuloendothelial system (34), the larger clearance observed with multiple dosing may be related to either an increase in phagocytosis by macrophages within the reticuloen-

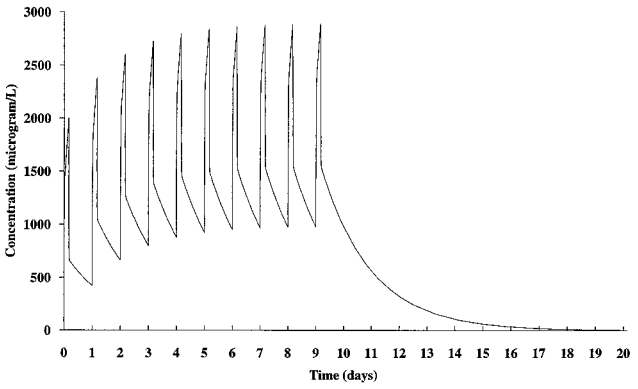

FIG. 5. Simulation of total plasma AmB concentrations following daily doses of 4.0 mg/kg of ABCD infused over 4 h.

TABLE 4. Summary statistics for ABCD pharmacokinetic parameter estimates

Parameter (unit)	Value for statistical index for group[a]			
	Children (<13 yr; $n = 5$)		Adults (13–64 yr; $n = 7$)	
	Median (range)	Mean (CV [%])	Median (range)	Mean (CV [%])
V_{ss} (liters/kg)	4.81 (1.99–6.47)	4.57 (36.3)	4.0 (2.35–6.81)	4.21 (32.9)
CL_t (liters/h/kg)	0.144 (0.114–0.167)	0.144 (15.4)	0.105 (0.0694–0.163)	0.111 (26.5)
λ_2 $t_{1/2}$ (h)	31.0 (14.8–45.0)	31.5 (40.3)	30.9 (23.1–41.6)	32.1 (17.4)
AUC_{ss} (μg/ml · h)	6.94 (5.96–8.80)	7.10 (16.2)	9.52 (6.15–14.4)	9.60 (27.0)

[a] Values for children and adults receiving either 7.0- or 7.5-mg/kg doses of ABCD. CV, coefficient of variation, calculated as (standard deviation/mean) × 100. AUC_{ss} is normalized to a 1-mg/kg/day dose of ABCD.

dothelial system or some other inducible eliminative process (32).

It is difficult to directly compare the pharmacokinetics of ABCD and DAmB because of the paucity of studies of the pharmacokinetics of AmB administered as DAmB. Furthermore, the available studies have utilized different patient populations and study designs, different assays (e.g., bioassays and high-performance liquid chromatography), and different approaches to pharmacokinetic data analysis. In addition, the curves for plasma drug concentration versus time have been characterized by both two- and three-compartment linear structural models. Nevertheless, the reported ranges of values for the volume of distribution, plasma clearance, and terminal $t_{1/2}$ of AmB are 0.5 to 4.0 liters/kg, 0.01 to 0.026 liter/h/kg, and 1 to 15 days, respectively. DAmB doses of 0.10 to 1.0 mg/kg, infused at a rate of 0.25 mg/kg/h, resulted in maximum plasma drug concentrations of 551 to 2,000 μg/liter (2, 9, 17, 23). The maximum achievable concentrations in plasma following a 1.0-mg/kg/h infusion rate for ABCD in this study ranged from 658 to 6,210 μg/liter at doses of 0.50 and 8.00 mg/kg, respectively.

The renal function-sparing effects of ABCD are evident from this study. There was no net change in renal function over the duration of ABCD treatment for the study population. In addition, there was no association between any pharmacokinetic exposure measure (i.e., AUC_{ss} or maximum or average concentration) of ABCD or other covariates (i.e., cyclosporine or gentamicin) and the percent change in CL_{CR}. Thus, it can be stated that ABCD (at these doses) does not alter renal function when administered alone or in combination with potentially nephrotoxic drugs to patients receiving bone marrow transplants.

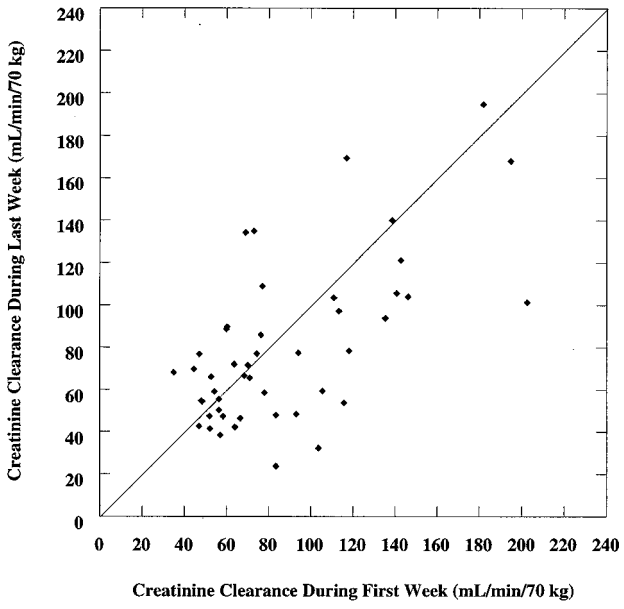

FIG. 6. Plot of values for CL_{CR} during the first versus last weeks of ABCD therapy.

ABCD's lack of renal toxicity is most likely associated with an alteration in the distribution characteristics of AmB. This hypothesis is supported by preclinical studies, in which it has been shown that renal toxicity is positively correlated with the amount of AmB in the kidney. For rats, the concentration of AmB in the kidneys of ABCD-treated animals was approximately sevenfold lower than that in DAmB-treated animals (7), which correlated with reduced renal toxicity. Further, dogs tolerated eightfold higher doses of ABCD before exhibiting any renal toxicity of the same severity as that produced by DAmB (8). The fact that less AmB is recovered from the kidney following ABCD administration than following DAmB administration may be related to the lipoprotein-binding characteristics of each formulation. It has been postulated that AmB bound to low-density lipoproteins may be responsible for the nephrotoxicity observed in vivo and that the disruption or decreased formation of this AmB–low-density lipoprotein complex could decrease the renal toxicity (3). Recently, it has been determined that changes in temperature and lipid composition of AmB do affect the binding characteristics of AmB to serum lipoproteins (35). In fact, after incubation of DAmB in serum at 37°C, the distribution of AmB was found to be similar for high- and low-density lipoproteins. However, upwards of 90% of AmB was associated with the high-density lipoprotein fraction following incubation of the lipid-based formulations. A similar finding was observed for ABCD following incubation in human plasma (13). There were 14- and 8-fold decreases in binding to the low- and high-density lipoprotein fractions, respectively, compared with that for the DAmB formulation. This greater affinity of the lipid-based AmB formulations for serum high-density lipoproteins may explain the lower amount of AmB recovered in the kidney.

This study suggests that ABCD can be administered safely as an antifungal agent to patients receiving bone marrow transplants. The lack of renal toxicity associated with ABCD will allow clinicians more flexibility in both the amount of drug administered and the duration of therapy. The usefulness of the pharmacokinetic parameter values derived from this study population will remain unclear until a relationship between the pharmacokinetics and pharmacodynamics of AmB is identified.

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