Pharmacokinetics, Safety, and Tolerability of Caspofungin in Children and Adolescents

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Caspofungin is a parenteral antifungal that inhibits beta-1,3-D-glucan synthesis. Although licensed for adult use, the appropriate caspofungin dosing regimen in pediatric patients is not yet known. We therefore investigated the pharmacokinetics and safety of caspofungin in pediatric patients. Thirty-nine children (ages 2 to 11 years) and adolescents (ages 12 to 17 years) with neutropenia were administered caspofungin using either a weight-based regimen (1 mg/kg of body weight/day) or a body surface area regimen (50 mg/m²/day or 70 mg/m²/day). Plasma samples for caspofungin profiles were collected on days 1 and 4. These results were compared to those from adults treated with either 50 or 70 mg/day for mucosal candidiasis. In children receiving 1 mg/kg/day (maximum, 50 mg/day), the area under the concentration-time curve over 24 h (AUC_{0–24}) was significantly smaller (46% after multiple doses) than that observed in adults receiving 50 mg/day ($P < 0.001$). In children and adolescents receiving 50 mg/m²/day (maximum, 70 mg/day), the AUC_{0–24} following multiple doses was similar to that for the exposure in adults receiving 50 mg/day. The AUC_{0–24} and concentration trough (at 24 h) in pediatric patients receiving the 50-mg/m² daily regimen were consistent across the range of ages. Caspofungin was generally well tolerated in this study. None of the patients developed a serious drug-related adverse event or were discontinued for toxicity. These results demonstrate that caspofungin at 1 mg/kg/day in pediatric patients is suboptimal. Caspofungin administration at 50 mg/m²/day provides a comparable exposure to that of adult patients treated with 50 mg/day.

Invasive fungal infections are an important cause of morbidity and mortality in immunocompromised pediatric patients (7–10, 13, 14, 22, 29, 30, 33). Caspofungin is a parenteral echinocandin antifungal agent with activity against both *Candida* (16, 20) and *Aspergillus* (1, 21) species. Caspofungin specifically targets the fungal cell wall and, thus, exerts activity against clinical isolates of *Candida* spp. with documented resistance to either the azoles or polyenes (3, 5, 6, 23, 27). The absence of this target in mammalian cells likely contributes to the favorable safety profile previously demonstrated for human adults (3, 17, 23, 27, 28). Comparative trials with adult patients have demonstrated that caspofungin is effective as a first-line agent for esophageal and invasive candidiasis (3, 17, 27, 28) and as a second-line agent for invasive aspergillosis (15). However, there is a paucity of data on the use of caspofungin in pediatric patients (11, 19), and little is known about the safety and pharmacokinetics of caspofungin therapy in children. In this report, we present the results from the first prospective, pediatric pharmacokinetic study involving caspofungin.

MATERIALS AND METHODS

Study population. The caspofungin pediatric pharmacokinetic study was an open-label, sequential-dose escalation study to evaluate the safety, tolerability, and pharmacokinetics of two dosing regimens of caspofungin for clinically stable neutropenic children or adolescents with a history of underlying hematological or solid-organ malignancy, hematopoietic stem cell transplantation, or aplastic anemia. The primary objective of the study was to identify a caspofungin dosing regimen for pediatric patients that yielded plasma concentrations similar to those observed in adult patients receiving the standard (50-mg/day) regimen.

Study participants were between the ages of 2 and 17 years and had new onsets of fever (temperature, $\geq 38^{\circ}\text{C}$) and neutropenia (absolute neutrophil count [ANC], $< 500/\text{mm}^3$). In this population of neutropenic patients, caspofungin was initiated within 24 h of the onset of fever (simultaneous with the administration of empirical antibacterial therapy). Hence, caspofungin was administered to a patient population for whom prophylactic antifungal therapy is routinely considered.

Exclusion criteria included the failure to meet all inclusion requirements, a history of allergy or serious reaction to echinocandins, or ongoing treatment with cyclosporine, rifampin, phenytoin, carbamazepine, phenobarbital, or other concomitant systemic antifungal agents (with the exception of prophylaxis with fluconazole). Abnormal laboratory values that disqualified patients from study participation were as follows: levels of total serum bilirubin or serum transaminases of three or more times the upper limit of normal (ULN), levels of serum alkaline phosphatase of five or more times the ULN, or an international normalization ratio of > 1.6 (or > 4.0 in patients receiving anticoagulant therapy). Patients with evidence of a proven or probable invasive fungal infection (4) at the time of enrollment were also excluded.

The study protocol was approved by the institutional review board of each participating institution, and written informed consent was obtained from the parent/guardian of each patient. Where applicable, assent was also obtained from those minors capable of understanding the study.

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Study design. At study enrollment, all patients were stratified into one of two different age groups: children between 2 and 11 years and adolescents between the ages of 12 and 17 years. Patients also were sequentially stratified based on the caspofungin dosing regimen. Initially, the study's intent was to enroll a total of 32 patients, including 8 patients in each of two age groups and at each of two mg/kg of body weight dosing regimens (caspofungin at 1.0 mg/kg/day and 1.5 mg/kg/day). However, it became evident during the course of the study that the caspofungin levels achieved in patients at 1 mg/kg/day (maximum, 50 mg/day) were suboptimal and both age and weight dependent. As a result, following the enrollment of the first nine patients at 1.0 mg/kg/day, the protocol was amended to evaluate two new caspofungin dosing regimens using a body surface area (BSA) approach: 50 mg/m²/day and 70 mg/m²/day. Again, the study's primary intention was to enroll 32 patients, including 8 patients in each of the two age groups and at each of two mg/m² dosing regimens (50 mg/m²/day and 70 mg/m²/day). Based on experience with adult patients, a 70-mg daily maximum was predefined for both the 50-mg/m² and 70-mg/m² daily regimens. The first group of patients received intravenous caspofungin daily at 50 mg/m². Once enrollment of at least eight patients was achieved at an age group, enrollment at 70 mg/m² was begun in that age group. With the exception of the noted change in dosing regimen, the overall design of the protocol was not changed.

Caspofungin was administered as a single daily dose infused over a 1-hour period. Caspofungin was to be continued until the patient recovered from the neutropenic episode (ANC, $\geq 250/\text{mm}^3$). However, if the patient remained febrile and neutropenic after 4 days of therapy or developed a proven or probable breakthrough fungal infection, caspofungin was to be discontinued and the patient was to receive thereafter intravenous amphotericin B (either conventional deoxycholate or a lipid formulation). The expected minimum duration of study therapy with caspofungin was 4 days, and the maximum duration of therapy was 28 days.

The time that the patients remained in the study included the time of caspofungin therapy and 14 days following the completion of study therapy. A daily assessment of fever and other signs and symptoms of a new breakthrough fungal infection was performed daily during the study therapy period. During the course of the study, patients were monitored for the development of adverse events; in particular, infusion-related events were carefully assessed following each dose of caspofungin therapy.

Pediatric pharmacokinetic sample collection and comparison to adult controls. Plasma was collected for determination of caspofungin concentrations from pediatric patients using a seven-point plasma schedule (predose and 1, 2, 4, 8, 12, and 24 h postdose) on days 1, 4, and 9 of caspofungin therapy. Plasma concentration trough (predose or at 24 h [C_{24}]) samples were also collected on treatment days 3, 7, 12, 14, 21, and 28. End-of-infusion and trough samples were collected 5 minutes and 23 h, respectively, following the completion of the 1-hour caspofungin infusion (C_1 and C_{24} determinations, respectively).

The caspofungin pharmacokinetics in pediatric patients was compared to the pharmacokinetics in two separate historical cohorts of adult patients: (i) patients with mucosal candidiasis and (ii) patients with persistent fever and neutropenia. Adult patients in the first comparative group with mucosal candidiasis (esophageal and/or oropharyngeal candidiasis) received a 50-mg or 70-mg daily dose of caspofungin during one of three phase II studies (protocols 003, 004, and 007) (3, 12, 27). Adult patients in the second comparative group with persistent fever and neutropenia received a 50-mg daily dose (following a loading dose of 70 mg on day 1) during the phase III study of caspofungin for empirical antifungal therapy (protocol 026) (31).

Patients with mucosal candidiasis (from protocols 004 and 007) served as the primary comparators, because the full pharmacokinetic sampling was available in these two clinical trials (3, 12). Profile sampling permitted comparisons of pharmacokinetic parameters, including end-of-infusion concentrations (C_1), trough concentrations (C_{24}), and area under the concentration-time curve (AUC) values. In both protocols 004 and 007, extensive pharmacokinetic samples (5-point and 11-point plasma profiles, respectively) were collected on day 1 and again after multiple doses (days 6 and 9 in protocol 004 and days 9 and 14 in protocol 007). Additionally, beta-phase half-life ($t_{1/2}$) data were available from protocol 007. For the trough comparisons, C_{24} data from protocol 003 were added to the data from protocols 004 and 007 (27). Comparisons of pediatric and adult pharmacokinetic data were made following both the first dose of caspofungin (day 1) and following multiple doses of caspofungin (time average of data from days 3 to 14 of therapy).

Comparisons also were made to adult patients with persistent fever and neutropenia who were enrolled in the caspofungin empirical therapy study (protocol 026) (31). This adult patient population was much closer in characteristics to the pediatric patients in this study (i.e., to patients with hematological malignancies or recipients of hematological stem cell transplantation). In this empirical ther-

apy study, peak and trough concentrations were performed on study therapy days 4, 7, and 14, and every 2 weeks thereafter (if the patient was still receiving study therapy). Hence, comparisons of pediatric and adult pharmacokinetic data from the empirical therapy study were made following multiple doses of caspofungin (time average of data from days 3 to 14 of therapy). As this adult study did not involve full pharmacokinetic sampling and the data became available only after the study was already initiated, the comparisons of the pharmacokinetics from the pediatric patients to these adult patients were considered exploratory in nature.

Bioanalytical and pharmacokinetic methods. BSA regimens were calculated based on the patients' heights and weights at the time of enrollment, based on the Mosteller formula (18), as follows: $\text{BSA (m}^2\text{)} = \{(\text{height [cm]} \times \text{weight [kg]}) / 3,600\}^{1/2}$.

Plasma samples for determination of caspofungin concentrations were stored at -70°C until analysis. Plasma concentrations of caspofungin were determined by high-pressure liquid chromatography with fluorescence detection as previously described (24). The plasma assay was modified slightly to allow for smaller sample volumes; 0.1 ml of plasma was used, with a resulting limit of quantitation of 125 ng/ml. In addition, a column-switching procedure was employed as described previously (25). Intraday variability (measured as the precision in terms of percent coefficient of variation) was 2.6% to 5.0%. Interday coefficients of variation ranged from 3.0% to 6.1%.

The AUC over the interval 0 to 24 h (AUC_{0-24}) was calculated by the linear-log trapezoidal method. For beta-phase $t_{1/2}$ assessments, an estimate of the β rate constant was calculated by weighted ($1/h^2$) nonlinear regression of the plasma concentration data at 8, 12, and 24 h using a monoexponential decay function. Half-lives (β -phase) were then computed as the quotient of $\ln(2)$ and the rate constant. Actual sampling times, as recorded by the investigator, were used for the calculation of both the half-lives and the AUCs. Evaluations of clearance (CL) were complicated by the lack of information on the gamma phase available either in the day 1 caspofungin plasma profile or in accumulation following approximately four multiple doses. Estimates of CL for the pediatric patients and adult comparators were determined as the quotients of doses and the day 1 AUC values from 0 h to infinity ($\text{AUC}_{0-\infty}$ values) (where the $\text{AUC}_{24-\infty}$ was extrapolated as the C_{24}/β rate constant). For three pediatric patients, day 1 $\text{AUC}_{0-\infty}$ s were not available, and the day 4 AUC_{0-24} s were used instead for this calculation. Based on full single-dose profile data obtained in a phase I study of 11 healthy adults at 70 or 100 mg (25), CL values calculated in this manner from 24-hour profile information on day 1 or day 4 are anticipated to be $\sim 7\%$ higher (range, 2 to 10%) than CL values which take into account data from the caspofungin gamma phase. However, because this degree of bias is small and likely to be similar across individuals, the CL values determined in this study from 24-hour profile data were judged to be useful for comparison purposes. As volume of distribution cannot be accurately assessed for caspofungin (26), this parameter was not determined.

In order to reduce the available multiple-dose pharmacokinetic data to a single parameter set and to allow comparisons between pediatric patients and adults for whom sampling on identical study days was not available, day 3-to-14 time-averaged parameters (for AUC_{0-24} , C_1 , or C_{24}) were determined as the geometric mean of all values for each individual parameter obtained during this time interval. The time-averaged half-life was calculated as the harmonic mean, and the time-averaged β rate constant was calculated as the arithmetic mean of all values obtained during the day 3 to 14 interval. In some instances, only one value was available during this interval, and, in those cases, that value was used as the mean. Although true steady-state pharmacokinetics is not achieved until 2 to 3 weeks of dosing, much of caspofungin accumulation occurs in the first few days of dosing (25). Thus, these day 3-to-14 time-averaged parameters are expected to be reasonably representative of steady state.

Statistical analysis and approaches. The primary objective for this study was to define the caspofungin dosing regimen for children and adolescents relative to that for adult patients receiving caspofungin at 50 mg/day for the treatment of mucosal candidiasis (from protocols 003, 004, and 007). Day 1 and time-averaged (days 3-to-14) AUC_{0-24} values were the primary pharmacokinetic parameters. The AUC data were natural log transformed prior to statistical analyses. A one-way analysis of variance (ANOVA) model having a five-level factor identifying the patient group (according to age and dose) was fitted to the transformed data. The geometric mean ratio (GMR) and associated 95% confidence intervals (CI) were derived from this ANOVA model. First, mean differences between the groups and the 95% CI for mean differences were calculated from the ANOVA. Then, these limits were exponentiated to obtain the GMR and associated 95% CI. Specifically, the ratios of the values for the following groups were evaluated: children at 50 mg/m²/day to adults at 50 mg/day, children at 70 mg/m²/day to adults at 70 mg/day, adolescents (12 to 17 years) at 50 mg/m²/day to adults at

TABLE 1. Baseline patient characteristics

Characteristic	No. of patients (%)					
	Caspofungin at 1.0 mg/kg; age, 2–11 yr (<i>n</i> = 7)	Caspofungin at 1.0 mg/kg; age, 12–17 yr (<i>n</i> = 2)	Caspofungin at 50 mg/m ² ; age, 2–11 yr (<i>n</i> = 10)	Caspofungin at 50 mg/m ² ; age, 12–17 yr (<i>n</i> = 8)	Caspofungin at 70 mg/m ² ; age, 2–11 yr (<i>n</i> = 12)	Total (<i>n</i> = 39)
Gender						
Male	4 (57.1)	0 (0.0)	5 (50.0)	6 (75.0)	5 (41.7)	20 (51.3)
Female	3 (42.9)	2 (100.0)	5 (50.0)	2 (25.0)	7 (58.3)	19 (48.7)
Race						
Caucasian	6 (85.7)	2 (100.0)	8 (80.0)	7 (87.5)	6 (50.0)	29 (74.4)
Hispanic	1 (14.3)	0 (0.0)	1 (10.0)	1 (12.5)	3 (25.0)	6 (15.4)
Other	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	3 (25.0)	4 (10.3)
Age (yr)						
2 to 6	5 (71.4)	0 (0.0)	3 (30.0)	0 (0.0)	10 (83.3)	18 (46.2)
7 to 11	2 (28.6)	0 (0.0)	7 (70.0)	0 (0.0)	2 (16.7)	11 (28.2)
12 to 14	0 (0.0)	2 (100.0)	0 (0.0)	5 (62.5)	0 (0.0)	7 (17.9)
15 to 17	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)	3 (7.7)
Mean	5.6	12.5	7.3	14.0	4.3	7.7
Range	4 to 7	12 to 13	2 to 11	12 to 16	2 to 10	2 to 16
Primary condition						
Acute lymphocytic leukemia	0 (0.0)	0 (0.0)	3 (30.0)	1 (12.5)	4 (33.3)	8 (20.5)
Acute myelogenous leukemia	2 (28.6)	1 (50.0)	2 (20.0)	5 (62.5)	3 (25.0)	13 (33.3)
Non-Hodgkin's lymphoma	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (2.6)
Neuroblastoma	4 (57.1)	0 (0.0)	1 (10.0)	0 (0.0)	3 (25.0)	8 (20.5)
Neuroectodermal tumor	1 (14.3)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (5.1)
Osteosarcoma/bone cancers	0 (0.0)	1 (50.0)	0 (0.0)	2 (25.0)	0 (0.0)	3 (7.7)
Other ^a	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	2 (16.7)	4 (10.3)
Transplant						
Allogeneic bone marrow	0 (0.0)	1 (50.0)	3 (30.0)	0 (0.0)	0 (0.0)	4 (10.3)
Autologous bone marrow	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	2 (16.7)	3 (7.7)
Autologous peripheral stem cell	5 (71.4)	1 (50.0)	1 (10.0)	1 (12.5)	3 (25.0)	11 (28.2)
Neutropenic status (no. of cells/mm ³) ^b						
<100	5 (71.4)	2 (100.0)	8 (80.0)	6 (75.0)	11 (91.7)	32 (82.1)
100 to 250	1 (14.3)	0 (0.0)	1 (10.0)	2 (25.0)	1 (8.3)	5 (12.8)
251 to 500	1 (14.3)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (5.1)

^a The other category includes one patient each with extragonadal primary germ cell tumor (mixed stage III), neuroblastoma, rhabdomyosarcoma, and thalassemia major.

^b The neutropenic status categories are mutually exclusive.

50 mg/day, and adolescents at 50 mg/m² to adults at 70 mg/day. Day 1 and time-averaged (days 3-to-14) *C*₁, *C*₂₄, and beta-phase constants were analyzed using the same methods as for the AUC_{0–24}, except that *C*₁ and *C*₂₄ data were log transformed prior to analysis, whereas beta-phase constants were untransformed. Formal beta-phase *t*_{1/2} comparisons between results for pediatric and adult patients were not performed. The same methods were used for the comparison of results for pediatric patients receiving 1 mg/kg/day regimen to those for the adult patients; the GMR (children 2 to 11 years at 1 mg/kg/day to adults at 50 mg/day) and 95% CI were constructed for each of the pharmacokinetic parameters (AUC_{0–24}, *C*₁, *C*₂₄).

Similar methods also were used to compare the pharmacokinetics in pediatric patients to that in the adult patients with persistent fever and neutropenia (from protocol 026) (31). For this comparison, only one GMR (children at 50 mg/m²/day to adults at 50 mg/day) could be calculated; the comparison was limited to *C*₁ and *C*₂₄ at the time-averaged (days 3-to-14) time point. AUC comparisons and beta-phase *t*_{1/2} assessments were not available from this adult set of data.

Plots of each of the parameters (AUC_{0–24}, *C*₁, and *C*₂₄) by patient age were also generated for patients receiving 50 mg/m²/day. The consistency of pharmacokinetics of caspofungin in children receiving BSA-scaled doses (50 and 70 mg/m²) across ages was also evaluated through a regression analysis. For each of the pharmacokinetic parameters, the data were log transformed prior to the analyses and included as the dependent variable in the model. The group to determine the interaction of age and dose was first tested to examine whether the slopes over age were different among different dose groups. The main effects would be dose group and age when an interaction was not statistically significant.

All patients who received at least one dose of caspofungin were included in the analysis of safety. The safety variables included the frequency of (i) clinical and laboratory adverse events, (ii) laboratory test values outside predefined clinically significant limits, and (iii) infusion-related events. No formal hypothesis testing of any of the safety endpoints was performed.

RESULTS

Enrollment. This caspofungin pediatric pharmacokinetic study was conducted in the United States between January 2001 and December 2002. Investigators at eight medical centers enrolled a total of 39 patients into the study.

Of note, only nine patients (seven children and two adolescents) were enrolled at 1 mg/kg/day. Once the AUC_{0–24} was found to be substantially lower than that obtained with 50 mg/day in adults, the study was amended to evaluate BSA (mg/m²) dosing. The 50-mg/m² cohorts for both the children (*n* = 10) and the adolescents (*n* = 8) were filled, as anticipated (Table 1). However, enrollment in the 70-mg/m² cohort was limited to the younger age group (children 2 to 11 years; *n* = 12). This is because six of the eight adolescents who received

TABLE 2. Caspofungin pharmacokinetics in neutropenic children and adolescents and in adult patients with mucosal candidiasis

Parameter	Children (2–11 yr)						Adolescents (12–17 yr)		Adults			
	Caspofungin, 1 mg/kg/day		Caspofungin, 50 mg/m ² /day		Caspofungin, 70 mg/m ² /day		Caspofungin, 50 mg/day		Caspofungin, 50 mg/day		Caspofungin, 70 mg/day	
	n	LSM ^a	n	LSM	n	LSM	n	LSM	n	LSM	n	LSM
Day 1												
AUC _{0–24} (μg · h/ml)	6	41.5	9	96.4	12	155	7	77.6	32	70.6	29	97.1
C ₁ (μg/ml)	6	6.59	10	13.9	12	19.5	8	8.95	38	7.67	37	10.0
C ₂₄ (μg/ml)	7	0.45	9	1.09	12	2.16	7	1.26	33	1.35	29	1.95
β-Phase t _{1/2} (h) ^b	6	7.4 (1.2)	9	7.6 (1.6)	11	8.9 (2.3)	7	10.5 (2.8)	6	11.7 (2.9)	6	12.2 (2.8)
CL (ml/min/m ²)	7	8.57	10	7.78	12	5.98	8	6.30	6	6.07	6	5.20
Days 3–14, time averaged ^c												
AUC _{0–24} (μg · h/ml)	7	56.3	9	115	9	161	8	117	38	103	35	154
C ₁ (μg/ml)	7	8.38	9	15.6	10	20.9	8	12.9	38	9.39	35	13.3
C ₂₄ (μg/ml)	7	0.63	9	1.46	9	2.47	8	2.15	60	2.01	57	3.33
β-Phase t _{1/2} (h) ^b	7	8.2 (1.0)	9	8.2 (2.4)	7	9.7 (2.0)	8	11.2 (1.7)	5	13.0 (1.9)	5	16.5 (7.0)

^a Least square means (LSM) are reported for AUC_{0–∞}, C₁, C₂₄, and CL.

^b Harmonic means (jackknife standard deviations) are reported for β-phase t_{1/2} s.

^c Time-averaged parameters determined as the geometric mean of all values obtained between days 3 and 14.

caspofungin at 50 mg/m²/day were actually receiving the maximum dose allowed by the protocol, namely, 70 mg/day.

Baseline characteristics. The overall distributions of male (51%) and female (49%) patients in this study were similar. An adequate distribution of patients also was noted across the range of ages within each stratum. The most common primary conditions reported across the entire range of patients were acute myelogenous leukemia (33%), acute lymphocytic leukemia (21%), and neuroblastoma (21%). Eleven (28%) and seven (18%) patients were recipients of peripheral stem cell or bone marrow transplantations, respectively. Of note, most patients (82%) entered the study profoundly neutropenic (ANC, <100 cells/mm³).

Duration of therapy. The mean duration of caspofungin therapy for all patients was 8.2 days (median, 5.5 days; range, 2 to 28 days). Fourteen of 39 (36%) patients received caspofungin for 4 (*n* = 10) or fewer (*n* = 4) days. At that time, many patients had either completed therapy (i.e., fever and neutropenia had resolved) or had discontinued caspofungin to begin

standard empirical antifungal therapy for persistent fever and neutropenia. Sixteen (41%) of the 39 patients received >7 days of therapy, including 5 (13%) patients who received >14 days of therapy.

Comparison of pharmacokinetic parameters between pediatric and adult patients. The pharmacokinetic parameters of caspofungin in pediatric patients are compared to those in adult patients with mucosal candidiasis in Tables 2 and 3 as the primary analysis. Comparison also is made of the results from the pediatric patients to the pharmacokinetic parameters of caspofungin in adults with persistent fever and neutropenia in Table 4 as an exploratory analysis.

Pharmacokinetics using weight-based dosing (at 1 mg/kg/day). Pharmacokinetic data were obtained from seven children (2 to 11 years) who received caspofungin at 1 mg/kg/day (Table 2). As shown in Table 3, the GMR of AUC_{0–24} values in these pediatric patients was less (41 to 46%) than that observed in adult patients receiving 50 mg/day for the treatment of mucosal candidiasis. These differences were statisti-

TABLE 3. Comparison of caspofungin pharmacokinetics in neutropenic children and adolescents to adult patients with mucosal candidiasis

Parameter	Children (2–11 yr)				Adolescents (12–17 yr)			
	Caspofungin at 1 mg/kg/day vs adults at 50 mg/day		Caspofungin at 50 mg/m ² /day vs adults at 50 mg/day		Caspofungin at 70 mg/m ² /day vs adults at 70 mg/day		Caspofungin at 50 mg/m ² /day vs adults at 50 mg/day	
	GMR (ped/adult) ^c	95% CI ^a	GMR (ped/adult)	95% CI	GMR (ped/adult)	95% CI	GMR (ped/adult)	95% CI
Day 1								
AUC _{0–24} (μg · hr/ml)	0.59	0.47, 0.73	1.37	1.09, 1.71	1.60	1.30, 1.95	1.10	0.86, 1.41
C ₁ (μg/ml)	0.86	0.68, 1.08	1.82	1.50, 2.22	1.94	1.61, 2.33	1.17	0.94, 1.45
C ₂₄ (μg/ml)	0.33	0.24, 0.45	0.81	0.58, 1.13	1.11	0.82, 1.51	0.94	0.65, 1.36
Days 3–14, time averaged ^b								
AUC _{0–24} (μg · hr/ml)	0.54	0.43, 0.68	1.11	0.90, 1.39	1.05	0.84, 1.31	1.13	0.90, 1.43
C ₁ (μg/ml)	0.89	0.71, 1.12	1.66	1.37, 2.01	1.57	1.31, 1.89	1.37	1.13, 1.68
C ₂₄ (μg/ml)	0.31	0.23, 0.43	0.72	0.54, 0.98	0.74	0.55, 1.00	1.07	0.78, 1.47

^a GMRs of the pediatric data versus adult data.

^b Time-averaged parameters determined as the geometric mean of all values obtained between days 3 and 14.

^c ped, pediatric patient.

TABLE 4. Comparison of caspofungin pharmacokinetics in children and adolescents^a

Day 3–14 time-averaged parameter	Pediatric patients		Historical adult controls		GMR (95% CI) (pediatric/adult)
	<i>n</i>	LSM (95% CI)	<i>n</i>	LSM (95% CI)	
Children (2–11 yr)					
<i>C</i> ₁ (μg/ml)	9	15.61 (12.13, 20.09)	119	7.39 (6.90, 7.92)	2.11 (1.63, 2.74)
<i>C</i> ₂₄ (μg/ml)	9	1.46 (1.07, 1.97)	117	1.41 (1.30, 1.54)	1.03 (0.75, 1.41)
Adolescents (12–17 yr)					
<i>C</i> ₁ (μg/ml)	8	12.90 (9.87, 16.85)	119	7.39 (6.90, 7.92)	1.74 (1.32, 2.30)
<i>C</i> ₂₄ (μg/ml)	8	2.15 (1.56, 2.97)	117	1.41 (1.30, 1.54)	1.52 (1.09, 2.12)

^a Children and adolescents received 50 mg/m²/day, and adult patients with persistent fever and neutropenia received 50 mg/day (following a 70-mg loading dose on day 1). Time-averaged parameters were determined as the geometric means of all values obtained between days 3 and 14. Least square means (LSM) and GMRs are reported for *C*₁ and *C*₂₄.

cally significant (P was <0.001 for both the day 1 and day 3-to-14 comparisons between pediatric and adult patients). Substantial, significant reductions were also obtained for *C*₂₄ (P was <0.001 for both the day 1 and day 3-to-14 comparisons) and β -phase half-life (P was 0.001 for both the day 1 and day 3-to-14 comparisons). *C*₂₄ decreased by 67% and 69%, and the β -phase half-life was reduced by 37% on both day 1 and days 3 to 14, in results for children relative to those for the adult controls. However, in both day 1 and day 3-to-14 groups, *C*₁ values were similar among the children and adults. Consistent with these results, the mean plasma concentration-time profiles from children receiving 1 mg/kg and adults receiving 50 mg are similar immediately postinfusion, after which point the profiles descend more rapidly in pediatric patients than in adult controls (Fig. 1).

Since only two adolescents were enrolled at 1 mg/kg/day, a formal comparison of the pharmacokinetic data from these two patients to those of the adults was not possible. However,

the plasma concentrations achieved in these two patients were also lower than those achieved in adults (data not shown).

These data indicate that 1.0 mg/kg/day is not an optimal dose for all children. Therefore, no further patients were enrolled into this cohort. A trend toward lower caspofungin concentrations in younger, smaller children relative to those in older, larger children suggested that weight-based (mg/kg) regimens would not be optimal for determining the pediatric dose of caspofungin. Pharmacokinetic projections of pediatric dosing (based on linear scaling of the 1-mg/kg data to BSA-based regimens) suggested that the pharmacokinetics would be more consistent with weight and age and that, in particular, a dose of 50 mg/m²/day would yield AUC values and trough concentrations commensurate to those noted in the adult cohort. Consequently, the study was amended to evaluate caspofungin using the BSA-scaled dosing.

Pharmacokinetics using BSA dosing (at 50 and 70 mg/m²/day) in children. Pharmacokinetic data from 10 children (2 to 11 years) who received caspofungin at 50 mg/m²/day were available for evaluation (Table 2). On day 1, the AUC_{0–24} for these pediatric patients was modestly (37%) greater than that observed in adult patients who received caspofungin at 50 mg/day for the treatment of mucosal candidiasis ($P = 0.007$). However, following multiple doses, the AUC_{0–24} for pediatric patients was similar to that of this adult cohort (Table 3 and Fig. 1). Although caspofungin AUC_{0–24} values were similar to or only slightly elevated in these children relative to the levels in adults, differences between the groups in other pharmacokinetic parameters were more apparent. As was also seen in the 1-mg/kg panel, the rate of decline in the mean plasma concentration-time profiles during the β -phase is faster in children than in adults (Fig. 1). The beta-phase half-life in children was 35% less on day 1 ($P = 0.002$) and 37% less on days 3 to 14 ($P = 0.002$) than those observed in adults. Consistent with this difference, the *C*₁ in children was greater than that observed in adults (82% on day 1, [$P < 0.001$]; 66% on days 3 to 14 [$P < 0.001$]) and day 3 to 14 *C*₂₄ in children was modestly less (28% [$P = 0.036$]) than that observed in adults with mucosal candidiasis. Day 1 *C*₂₄s were similar in children and adults.

A comparison of these pediatric data versus adult data from patients with persistent fever and neutropenia (from the caspofungin empirical therapy study [31]) also demonstrated a greater day 3-to-14 *C*₁ in these pediatric patients than that observed in adults (111% increase [$P < 0.001$]). However, day 3-to-14 *C*₂₄

FIG. 1. Mean caspofungin plasma concentration-time profiles in children and adolescents with neutropenia and adult patients with mucosal candidiasis. Profiles for pediatric patients are from day 4 of therapy, and profiles for adults are from day 9 of therapy.

FIG. 2. Individual caspofungin pharmacokinetics following multiple doses in children and adolescents receiving caspofungin at 50 mg/m²/day, adults with mucosal candidiasis receiving caspofungin at 50 mg/day, and adults with persistent fever and neutropenia receiving caspofungin at 50 mg/day.

values in children and these adults were similar (Table 4 and Fig. 2).

Pharmacokinetic data from 12 children who received caspofungin at 70 mg/m²/day were also available for evaluation (Table 2). These patients were compared to adult patients receiving 70 mg/day for the treatment of mucosal candidiasis (Fig. 2 and Table 3). In general, the results from comparisons of the pharmacokinetic parameters (AUC_{0-24} , C_1 , and C_{24}) at these higher doses (pediatric dose, 70 mg/m²/day; adult dose, 70 mg/day) were similar to the results from comparisons at the lower doses (pediatric dose, 50 mg/m²/day; adult dose, 50 mg/day).

Pharmacokinetics using BSA dosing (at 50 mg/m²/day) in adolescents. Pharmacokinetic data from eight adolescents (12 to 17 years of age) who received caspofungin at 50 mg/m²/day were also evaluated (Table 2). On day 1 and following multiple doses, there were no appreciable differences in AUC_{0-24} between the results from adolescents and those of adults receiving 50 mg/day for the treatment of mucosal candidiasis (Table 3 and Fig. 2). The plasma concentration-time profile in

these adolescents was generally similar in shape to that obtained in adult patients (Fig. 1). Consistent with the results for AUC_{0-24} , the other pharmacokinetic parameters (C_1 , C_{24} , and β -phase half-life) were generally similar between adolescents receiving 50 mg/m²/day and adults receiving 50 mg/day (Fig. 1). There was a tendency for the C_1 in adolescents to be somewhat greater and for β -phase half-life in adolescents to be somewhat less than that observed in adults; however, with the exception of day 3-to-14 C_1 s ($P = 0.002$), there were no statistically significant differences in pharmacokinetics between the adolescents and adults.

Most of the adolescent patients (six of eight) received the maximum dose allowed in the study (70 mg/day), and all received >50 mg/day. Therefore, an exploratory comparison of pharmacokinetics in these patients and historical pharmacokinetic data for adults at 70 mg/day, a dose much closer to the average dose that the adolescents received, was performed. This comparison indicates that plasma concentrations in adolescents are less than those observed in adults receiving similar doses, particularly for AUC_{0-24} (20% and 24% less than in adults on day 1 and days 3 to 14, respectively) and C_{24} (35% less on both day 1 and days 3 to 14). This suggests that the adolescents require somewhat higher absolute doses, as are achieved by a dosing regimen of 50 mg/m²/day (70 mg/day maximum), to obtain pharmacokinetics similar to that obtained in adults at 50 mg/day.

A comparison of this adolescent data versus adult data from patients with persistent fever and neutropenia (from the caspofungin empirical therapy study [31]) indicated that day 3-to-14 C_1 s and C_{24} s in adolescents were greater (74% [$P < 0.001$] and 52% [$P = 0.014$], respectively) than those observed in this adult population (Table 4).

Consistency of results across ages. Caspofungin pharmacokinetic results were consistent in pediatric patients across ages with BSA-scaled dosing for pediatric patients receiving 50 mg/m²/day. The effect of age also was evaluated through a regression analysis of all data from BSA-scaled doses with an adjustment for dosing regimens (50 mg/m²/day versus 70 mg/m²/day). The 95% CI for the estimates of the slope (β_1) of the relationship between age and the log-transformed pharmacokinetics for AUC_{0-24} and C_{24} both on day 1 and after multiple doses contain zero, indicating that no statistically significant variations in these parameters with age were identified in the data from pediatric patients receiving BSA-scaled doses. However, the 95% CI for the estimates of β_1 for C_1 on day 1 and after multiple doses fell entirely below zero, indicating that statistically significant decreases in the end-of-infusion concentrations of caspofungin with increasing age were identified.

The variation in CL with age in adult and pediatric patients, pooled across all dosing regimens, is illustrated in Fig. 3. CL, on an absolute scale, increases with age, with older adolescents having CL values in the upper range of adult values. Weight-normalized CL decreases with increasing age in the pediatric population. Body surface area-normalized CL was consistent across the age range of 2 to 16 years evaluated in this study. Of note, BSA-normalized CL in the pediatric patients averaged 7.4 ml/min/m², which was 27.8% higher than the average value in adult patients (5.8 ml/min/m²).

Breakthrough invasive fungal infections. Although efficacy was not specifically assessed in this trial, patients were closely

FIG. 3. Caspofungin CL versus age in pediatric patients and adult patients with mucosal candidiasis. The slope of the CL linear regression line (top) is 0.0391, the slope of the weight-normalized CL linear regression line (middle) is -0.0152 , and the slope of the BSA-normalized CL linear regression line (bottom) is 0.00056 .

evaluated for the development of a breakthrough fungal infection during the course of the study. Overall, a total of 2 (5.1%) of the 39 patients who received caspofungin developed a proven or probable breakthrough fungal infection either during the study therapy period or in the 14-day posttherapy follow-up period. Both patients were adolescents who received caspofungin at $50 \text{ mg/m}^2/\text{day}$ (daily doses of 60 and 70 mg in the two patients) and who developed a proven filamentous fungal infection. Invasive pulmonary aspergillosis due to *Aspergillus flavus* developed in one patient, and pulmonary zygomycosis developed in the other. The caspofungin concentrations achieved in these patients were in the mid-to-upper range of values observed in this study.

Safety and tolerability. Caspofungin was generally well tolerated in this study. Of the 39 patients, 5 (12.8%) patients reported one or more drug-related clinical adverse experiences: one patient each with fever/rigors, diarrhea, phlebitis, proteinuria, and transient extremity rash. Similarly, two (5.1%) of the 39 patients reported one or more drug-related laboratory adverse experiences: one patient each with hypokalemia and increased serum aspartate transaminase. The frequency of drug-related clinical and laboratory adverse events was not

concentrated within one particular age group or treatment regimen but, in general, was distributed among a number of the different treatment groups. Notably, none of the drug-related adverse events were considered serious or led to study discontinuation of caspofungin.

In general, the proportion of patients fulfilling the criteria for various clinically significant renal or hepatic abnormalities was also relatively low. The most common clinically significant laboratory finding, occurring in six (16.7%) patients, was a decrease in creatinine clearance (CL_{CR}) to 75% of the baseline value. In all cases, the associated decrease in CL_{CR} occurred in patients receiving aminoglycoside therapy or in patients having recently received cytotoxic chemotherapy. Notably, none of the six patients had a decrease in CL_{CR} to 50% of the baseline value while in the study. Cases exceeding the criteria for elevated serum transaminase levels (an aspartate transaminase or alanine aminotransferase level of >2.5 times the ULN or >2.5 times the baseline value) were uncommon (8.3 and 11.1%, respectively).

Systemic reactions also were assessed by the daily reporting or evaluation of specific infusion-related events. Overall, infusion-related adverse events were noted in only two (5.1%) of the patients. One patient developed nervous indigestion, fever, and chills during the caspofungin infusion; the other developed a transient erythematous rash on his fingers and toes during the initial infusion of caspofungin. All findings were mild in intensity.

DISCUSSION

Herein, we describe the results of the first prospective trial to evaluate the use of caspofungin in pediatric patients. Several important pharmacokinetic findings in this study warrant discussion. First, this study clearly demonstrates that caspofungin dosing at 1 mg/kg results in suboptimal concentrations in pediatric patients. The AUC_{0-24} , C_{24} , and half-life in the pediatric patients were significantly less than those observed in adults with mucosal candidiasis receiving the approved 50-mg daily dose. These findings raised concerns regarding the appropriateness of weight-based scaling of caspofungin doses for pediatric patients. Variations noted in the pharmacokinetic results with both weight and age suggested that weight-based dosing of caspofungin would not provide consistent pharmacokinetics across age. The reduction in weight-normalized CL with increasing age further supports the unsuitability of weight-based dosing of caspofungin. On the basis of this analysis, the current study was amended to evaluate BSA-based dosing of caspofungin in pediatric patients. The lack of statistically significant variations between adult and pediatric patients in caspofungin AUC_{0-24} and C_{24} with mg/m^2 regimens confirms that BSA-scaled dosing of caspofungin is appropriate for pediatric patients. The appropriateness of BSA-scaled dosing for caspofungin is further supported by the consistency of BSA-normalized CL values with age in the pediatric patients.

In children (ages 2 to 11 years) receiving caspofungin at $50 \text{ mg/m}^2/\text{day}$, the AUC_{0-24} after multiple doses was comparable to that in adults with mucosal candidiasis receiving a regimen of 50 mg/day . Although the AUC_{0-24} on day 1 in children was somewhat greater than that observed in adults with mucosal candidiasis, it is not expected that exceeding the

FIG. 4. Effects of 1-mg/kg and 50-mg/m² dosages on the total dose administered to pediatric patients receiving caspofungin. The BSA was calculated from the 50th-percentile height and weight parameters of standard nomograms of normal males aged 2 through 17 years. The total dose of caspofungin was then calculated as a function of weight and BSA.

50-mg adult exposure for the first few days of therapy prior to reaching steady state would be clinically meaningful. This is based on the knowledge that the exposure in children is within the overall range evaluated in adults; moreover, dose-limiting toxicities have not been seen in adults receiving higher doses of caspofungin. Furthermore, it should be recognized that the AUC_{0–24} values in these children on day 1 were still less than those seen in adults at steady state for these comparisons. Moreover, the drug's half-life in the children was 30 to 40% shorter than that in adults, and in children relative to adults, C_1 was increased (~60%) and C_{24} decreased (~27%) after multiple doses. The difference in half-life does not permit the identification of a once-daily pediatric dose that would provide values commensurate to those for adults for all three parameters (AUC_{0–24}, C_1 , and C_{24}).

The critical pharmacokinetic parameter for efficacy of caspofungin and other echinocandins appears to be concentration dependent, rather than time dependent. Andes et al. (2) and Wiederhold et al. (32) described the maximum concentration of drug in serum (C_{max})/MIC as the key pharmacodynamic variable against experimental murine candidiasis and aspergillosis, respectively. Louie et al. reported that the AUC_{0–24} may be the critical parameter for efficacy in a nonneutropenic mouse model of candidiasis (A. Louie, M. Deziel, W. Liu, M. Drusano, T. Gumbo, and G. L. Drusano, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1572, 2003). Furthermore, the comparison of the data from young children to data from adults with persistent fever and neutropenia (from the caspofungin empirical therapy study) suggests that 50 mg/m²/day in children achieves a comparable C_{24} to that in adults receiving 50 mg/day. This is particularly relevant be-

cause the pediatric patients enrolled in the current study and the adult patients enrolled in the empirical therapy study had similar demographics (31). Thus, the modest reduction in C_{24} noted in children relative to adults with mucosal candidiasis may be due to differences in the underlying disease characteristics in the compared patient groups. Although more-frequent dosing could potentially achieve peak and trough concentrations in children that are more similar to those observed in adults, the favorable safety profile of caspofungin allows for children to receive a more convenient once-daily dose that readily achieves the drug exposures found to be efficacious in adult trials.

Taken together, these results suggest that plasma concentrations are not reduced to a clinically meaningful extent at any time during the 50-mg/m² dosing interval in young children relative to those in adults receiving 50 mg/day. The increase in C_1 in children receiving 50 mg/m²/day relative to that in adults receiving 50 mg/day is also unlikely to be clinically meaningful, since the C_1 achieved in children receiving 50 mg/m²/day was roughly comparable to values obtained at 70 mg/day in adult patients with mucosal candidiasis or in healthy adult subjects (25). A dose of 70 mg/day has been generally well tolerated in adults (3, 23, 27).

The shorter caspofungin beta-phase half-life observed in these children relative to that in adults is most likely due to an increase in the relative rate of plasma CL in these children, as suggested by both the weight-normalized and BSA-normalized CL comparisons in Fig. 3. Previous results from a single-dose disposition study of [³H]caspofungin in adults indicate that little metabolism or excretion occurs during the first 24 h postdose and that uptake of drug into tissue cells, including

hepatocytes, is the mechanism controlling the decline of the drug level observed during the beta phase (26). These findings suggest that the intrinsic rate of caspofungin uptake transport is increased in children relative to adults. Very little is known about the maturation of uptake transport in children. Thus, differences in the levels of expression or the activities of transporters may contribute to the observed pharmacokinetic differences. However, other factors, such as relative hepatic size and blood flow, may also play an integral role in differential CLs between pediatric and adult patients.

This study also documents that adolescents require the higher doses achieved with a dose of 50 mg/m²/day (maximum, 70 mg/day) to obtain pharmacokinetic results similar to those obtained in adults receiving the standard 50-mg daily regimen. On both day 1 and following multiple doses, the pharmacokinetic results achieved in adolescents following a 50-mg/m² daily dose were generally comparable to those seen in adults receiving the 50-mg daily dose of caspofungin. However, in this study, all adolescents received doses of >50 mg/day, with six of eight receiving the maximum 70-mg daily dose. The caspofungin plasma concentrations in adolescents were reduced relative to those in adults receiving the 70-mg daily regimen. This finding is consistent with the higher absolute CL in adolescents than in adults and with the ~28% increase in BSA-normalized CL in pediatric patients relative to that in adults. Trends in the data for adolescents towards a higher *C*₁ and shorter half-life relative to those for adults are consistent with the alterations in caspofungin pharmacokinetics noted in younger children. These alterations, however, are of much smaller magnitude in the adolescents than in younger children.

We further sought to understand the effects of the 1-mg/kg and the 50-mg/m² dosages on the total dose administered to pediatric patients receiving caspofungin. Using standard growth curves of pediatric males, we tabulated the 50th percentile of height and weight for each year from 2 through 17 years. The BSA was then calculated from these height and weight parameters. The total dose of caspofungin for ages 2 to 17 years was then calculated as a function of weight and BSA (Fig. 4).

Finally, the safety and tolerability of caspofungin in these pediatric patients should be underscored. The frequency of drug-related adverse events or clinically significant laboratory abnormalities following caspofungin use was relatively low in children and adolescents. No specific drug-related adverse event was seen in more than one patient. Of particular note, none of the patients developed a serious, drug-related adverse event or required discontinuation of the caspofungin as a result of a drug-related adverse event. Systemic infusion-related events were also seldom observed. In general, the overall safety profile in this study is consistent with that which has been previously noted for caspofungin use in adult patients enrolled in other caspofungin clinical studies (3, 15, 17, 23, 27–28).

In summary, this study represents the first evaluation of caspofungin in pediatric patients. The pharmacokinetic results of this study help to establish that a daily 1-mg/kg caspofungin dose results in suboptimal levels in pediatric patients. These results also confirm that the use of a BSA-based dosing regimen is a more appropriate method for dosing pediatric patients between the ages of 2 and 17 years. Specifically, a dose of 50 mg/m²/day (70 mg/day maximum) in children and ado-

lescents provides comparable exposure to that obtained in adults receiving a standard 50-mg daily regimen. The results of this study serve as the basis for the selection of a BSA dosing regimen of caspofungin for future pediatric studies involving younger age groups.

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