
Safety and Pharmacokinetics of Higher Doses of Caspofungin in Healthy Adult Participants

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Caspofungin was the first in a new class of antifungal agents (echinocandins) indicated for the treatment of primary and refractory fungal infections. Higher doses of caspofungin may provide another option for patients who have failed caspofungin or other antifungal therapy. This study evaluated the safety, tolerability, and pharmacokinetics of single 150- and 210-mg doses of caspofungin in 16 healthy participants and 100 mg/d for 21 days in 20 healthy participants. Other than infusion site reactions and 1 reversible elevation in alanine aminotransferase ($\geq 2\times$ and $<4\times$ upper limit of normal), caspofungin was generally well tolerated. Geometric mean $AUC_{0-\infty}$ after single 150- and 210-mg doses was 279.7 and 374.9 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively; peak concentrations were 29.4 and 33.5 $\mu\text{g}/\text{mL}$, respectively; and 24-hour postdose concentrations

were 2.8 and 4.2 $\mu\text{g}/\text{mL}$, respectively. Steady state was achieved in the third week of dosing. Following multiple 100-mg doses of caspofungin, day 21 geometric mean AUC_{0-24} was 227.4 $\mu\text{g}\cdot\text{h}/\text{mL}$, peak concentration was 20.9 $\mu\text{g}/\text{mL}$, and trough concentration was 4.7 $\mu\text{g}/\text{mL}$. Beta-phase $t_{1/2}$ was ~ 8 to ~ 13 hours. Caspofungin pharmacokinetics at these higher doses were dose proportional to and consistent with those observed at lower doses, suggesting a modest nonlinearity of increased accumulation with dose, which was considered not clinically meaningful.

Keywords: caspofungin; high dose; pharmacokinetics; safety; tolerability

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Caspofungin was the first in a new class of antifungal agents known as echinocandins, which exert their antifungal effect through noncompetitive inhibition of (1,3)- β -D-glucan biosynthesis. Caspofungin displays concentration-dependent activity *in vitro*^{1,2} and in animal models^{3,4} of invasive candidiasis and invasive aspergillosis. Caspofungin is approved for the treatment of esophageal

candidiasis⁵ and invasive candidiasis (including candidemia)^{6,7} and as empirical therapy of suspected fungal infections in patients with persistent fever and neutropenia.⁸ Caspofungin is also approved for the treatment of invasive aspergillosis in patients refractory or intolerant to existing therapies; response rates in this population tend to be lower in patients with neutropenia, extrapulmonary disease, or prior hematopoietic stem cell transplant (HCST).⁹

The recommended dose for treating invasive fungal infections is 70 mg on day 1 followed by a maintenance dose of 50 mg/d.¹⁰ Higher doses of caspofungin may provide greater local concentrations in infected tissues and may therefore lead to improved therapeutic outcomes in certain populations, such as immunocompromised patients,¹¹ difficult-to-treat sites of infection (eg, *Candida* endophthalmitis), or recalcitrant infections (including those initially unresponsive to standard caspofungin doses). The purpose of the current study was to evaluate the safety, tolerability, and pharmacokinetics of caspofungin in healthy participants after

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single 150-mg and 210-mg doses and after 100 mg/d for 21 days.

MATERIALS AND METHODS

This single-center study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from each participant before any study procedure was performed. The study was approved by the Research Consultants' Review Committee in Austin, Texas. Participants were men and women, 18 to 45 years of age, of nonreproductive potential who were nonsmokers, weighed at least 66 kg, were within 30% of ideal body weight, and were in generally good health. Participants with abnormal liver function tests were excluded. Use of alcoholic beverages, prescription or nonprescription medications, and excessive consumption of caffeinated products were not permitted during the study. The study had 2 parts, each consisting of different participants. Each panel of part I also consisted of different participants, as described below.

Single-dose evaluation (part I). This was a randomized, double-blind, placebo-controlled study of 16 healthy adult men and women who received single 150-mg (panel A) or 210-mg (panel B) doses of caspofungin or matching placebo by 1-hour intravenous infusion. In each panel, 6 participants received caspofungin and 2 received placebo. Participants remained at the clinical research unit (CRU) for 24 hours after drug administration. Blood samples for determination of caspofungin plasma concentrations were collected at predose (0 hours) and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, and 12 hours after the start of infusion. Additional safety evaluations and blood sampling for pharmacokinetic analysis were collected on days 2, 3, 4, 5, 7, 10, and 14.

Multiple-dose evaluation (part II). This was a randomized, double-blind, placebo-controlled study of 20 healthy adult men and women who received 100-mg intravenous doses of caspofungin ($n = 15$) or matching placebo ($n = 5$) given over 1 hour once daily for 21 days. Participants remained in the CRU from day 1 (first day of drug administration) until the morning of day 22 (24 hours after the final dose). Participants returned to the CRU for safety evaluations (including liver function tests) and pharmacokinetic evaluations for 4 weeks after the final dose of study drug. Blood samples for caspofungin plasma concentrations (full profile) were obtained at predose (0 hours) and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6,

9, 12, and 24 hours after the start of infusion on days 1, 14, and 21. Blood samples for trough drug concentrations were also collected on specified days during drug administration and on days 22 to 49 (while participants were off study drug).

Bioanalytical and Pharmacokinetic Methods

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 detection¹² and a column-switching procedure¹³ as previously described. The limit of quantitation was 25 ng/mL.

Plasma terminal rate constants, β and γ , were calculated by weighted ($1/y^2$) nonlinear regression of the terminal plasma concentration data on day 1 and day 21 using a biexponential decay function. The onset of the log-linear β -phase was determined visually for each participant. Half-lives (β - and γ -phase) were computed as the quotient of $\ln(2)$ and the respective rate constant. The accumulation half-life was calculated from the accumulation ratio, where accumulation is equal to $1/(1 - e^{-k\tau})$; k is $\ln(2)/t_{1/2, \text{accumulation}}$, and τ is the dosing interval.

The area under the concentration-time curve (AUC) from time = 0 to last quantifiable concentration (AUC_{0-t}) for single-dose profiles and to 24 hours postdose ($\text{AUC}_{0-24 \text{ h}}$) for multiple-dose profiles was calculated by the linear-log trapezoidal method. For single-dose profiles, the AUC from the last quantifiable concentration to infinity ($\text{AUC}_{t-\infty}$) was extrapolated as the quotient of the last quantifiable concentration and the terminal rate constant; $\text{AUC}_{0-\infty}$ was determined as the sum of AUC_{0-t} and $\text{AUC}_{t-\infty}$. Clearance after administration of single doses was calculated as the quotient of dose and $\text{AUC}_{0-\infty}$. The fraction of total AUC attributed to each of the alpha, beta, and gamma phases was determined by fitting a triexponential equation to the concentration-time profiles (beginning at the stop of infusion), then integrating each term of the equation separately after adjusting the y-intercepts for adjusting for infusion duration. In 5 participants whose $C_{1 \text{ h}}$ sample collection differed by more than 1 minute, the end-of-infusion concentration was determined by fitting the plasma concentration time data to a 3-compartment linear model along with the plasma concentration data in the AUC calculations. Otherwise, the actual sampling times were used for calculation of pharmacokinetic parameters.

Statistical Analyses

Single-dose evaluation (part I). Summary statistics included the geometric means and corresponding 90% confidence interval (CI) for $AUC_{0-24\text{ h}}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ after administration of single intravenous 150-mg or 210-mg doses of caspofungin. The dose proportionality of caspofungin $AUC_{0-\infty}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ over the dose range of 5 to 210 mg was assessed by fitting a power law model under a mixed-effect modeling approach. For each natural log-transformed pharmacokinetic parameter, the mixed-effect model includes continuous covariate $\ln(\text{dose})$ and a random effect for participant. In each analysis, the geometric mean and 90% CI were generated for the slope (β) of $\ln(\text{dose})$.

Multiple-dose evaluation (part II). The geometric mean ratio (GMR; day 21/day 1) for the $AUC_{0-24\text{ h}}$ of caspofungin was calculated to determine whether the secondary hypothesis would be supported. AUC data were natural log-transformed, and a 2-sided 90% CI (equivalent to a 1-sided 95% CI) was then constructed for the mean difference (day 21 to day 1) on the log scale. The limits of this CI were then exponentiated to construct the 90% CI for the GMR (day 21/day 1). Summary statistics were computed, including the geometric means and 90% CI for $AUC_{0-24\text{ h}}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ on days 1, 14, and 21 of administration. Accumulation on day 14 was evaluated by calculating the GMR (day 14/day 1) and corresponding 90% CI. Summary statistics for half-lives after administration of caspofungin on day 21 also were computed. Determination of whether steady state was achieved by day 14 was evaluated by comparing pharmacokinetic parameters (log-transformed $AUC_{0-24\text{ h}}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$) at day 14 and day 21. An estimate of the within-subject variance was obtained by calculating the mean square error (MSE) from an analysis of variance (ANOVA) model containing terms for subject and day (days 14 and 21). For each pharmacokinetic parameter, a 90% CI was calculated for the difference in least square means on the log scale using the MSE from the ANOVA model. The difference in least square means and corresponding 90% CIs was exponentiated to obtain the GMR and 90% confidence limits on the original scale. In addition, assessment of whether steady state was achieved was conducted by estimating the linear trend of $C_{24\text{ h}}$ over successive day ranges from day 1 to day 21. An ANOVA model was fitted with terms of subject and day (day 1 through day 21). Beginning with day 1, data were evaluated to

determine the first day on which there was no statistically significant trend in $C_{24\text{ h}}$ from that day to day 21 of administration. Historical data from participants who received single 5- to 100-mg doses of caspofungin¹³ were compared with the corresponding pharmacokinetic parameters obtained in part I of the current study. Historical data from participants who received multiple 15- to 70-mg doses of caspofungin^{13,14} were compared with the corresponding pharmacokinetic parameters obtained in part II of the current study.

RESULTS

Single-Dose Study (Part I)

Safety. All 16 participants were included in the safety analyses. Twelve participants received caspofungin (6 at 150 mg; 6 at 210 mg), and 4 received matching placebo (2 in each dose group). There were no serious clinical adverse events, and no participant discontinued study participation because of a clinical adverse event. Three participants who received the 150-mg dose reported 7 adverse events: neck pain, tonsillar enlargement, skin erythema, headache (2 episodes), ecchymosis, and constipation; all were considered mild, except for 1 headache that was moderate, and all were rated by the investigator as probably not related to study drug. One participant who received the 210-mg dose reported mild pruritus (lasting 5 minutes) and rash and erythema (lasting 2 hours) that were considered probably related to study drug; this participant recovered from these events without treatment. One participant who received placebo had an elevated aspartate aminotransferase (AST) of 73 IU/L (normal range, 10-42 IU/L) on day 5 of the study, but this returned to the normal range (24 IU/L) by day 14.

Pharmacokinetics. Caspofungin plasma concentrations achieved after doses of 150 and 210 mg, as characterized by $AUC_{0-\infty}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ (Table I), exceeded those previously obtained at lower doses.¹³ The systemic plasma clearance after administration of 150-mg and 210-mg doses was similar to historical data at lower doses (geometric mean clearances ranged from 9.9 to 12.4 mL/min at doses between 5 and 100 mg¹³) but with a trend toward slightly reduced clearance at the 150-mg and 210-mg doses. The plasma concentration-time profiles of caspofungin after administration of 150-mg and 210-mg doses were similar to those previously obtained at 5- to 100-mg doses (Figure 1). After a single 1-hour

Table I Geometric Mean (90% Confidence Interval) of Pharmacokinetic Parameters of Caspofungin After Single 150- or 210-mg Doses of Caspofungin Infused Over 1 Hour

Dose, mg	n	AUC _{0-∞} , µg·h/mL	C _{1h} , µg/mL	C _{24h} , µg/mL	Clearance, mL/min	β-Phase Half-Life, h ^a
150	6	279.7 (226.7, 345.1)	29.4 (26.6, 32.5)	2.8 (2.1, 3.9)	8.9 (7.2, 11.0)	8.1 ± 1.0
210	6	374.9 (329.2, 426.9)	33.5 (29.1, 38.7)	4.2 (3.2, 5.5)	9.3 (8.2, 10.6)	9.2 ± 2.3

a. Harmonic mean (jackknife standard deviation) reported for half-life.

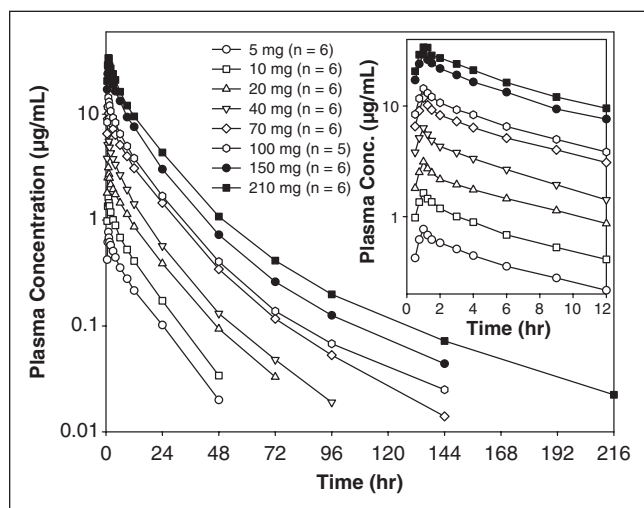


Figure 1. Mean-plasma concentration profiles of caspofungin following single 1-hour intravenous infusions of 5 to 210 mg. Data from current study shown in black symbols and historical data from Protocol 001 (Single, Rising Dose Study in Healthy Subjects), shown in white symbols.

infusion, plasma concentrations of caspofungin declined in a polyphasic manner. A short α -phase was seen immediately postinfusion, followed by a dominant β -phase that exhibited clear log-linear behavior from ~6 to ~48 hours postdose, after which an additional longer half-life γ -phase was evident at doses where the plasma concentrations remained above the limit of quantitation for more than 3 days. The β -phase half-lives after administration of 150-mg and 210-mg doses were similar to estimates previously obtained at lower doses (harmonic mean β -phase half-lives ranged from 8.6 to 10.7 at doses from 5 to 100 mg¹³). This observation also suggested that approximate linear pharmacokinetics continued to be maintained after administration of higher doses. Both a visual (Figure 2) and statistical assessment of dose proportionality of caspofungin AUC_{0-∞}, C_{1h}, and C_{24h} over the dose range of 5 to 210 mg was performed. In the case of perfect dose proportionality, a power law model fit to log-transformed data

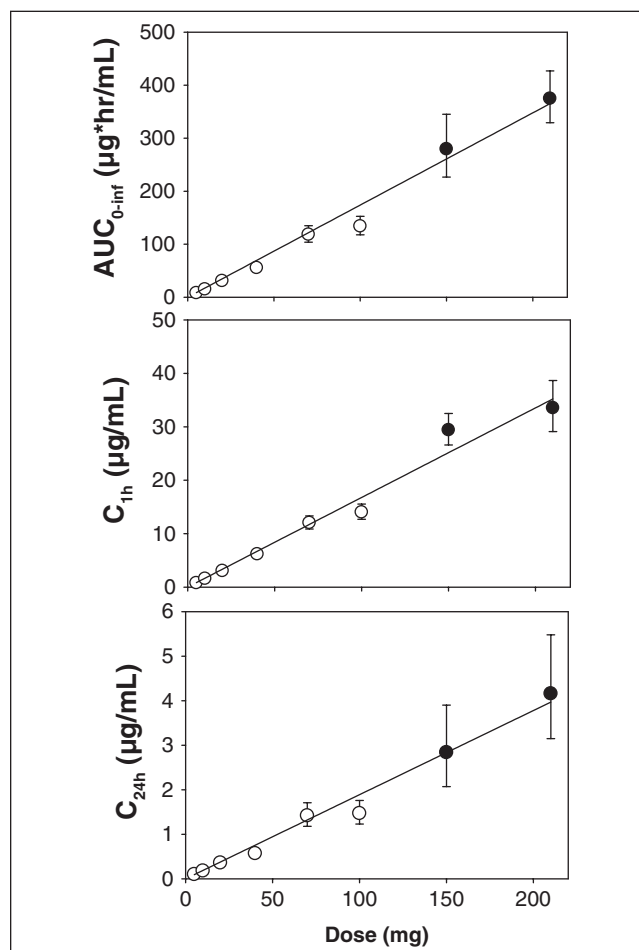


Figure 2. Geometric mean AUC_{0-∞}, C_{1h}, and C_{24h} (with 90% confidence intervals) vs dose following single 1-hour intravenous infusions of caspofungin. Data from current study shown in black symbols and historical data from Protocol 001 (Single, Rising Dose Study in Healthy Subjects), shown in white symbols. Lines shown were fit to the geometric mean data with a linear regression.

had a slope of $\ln(\text{dose})$ equal to 1.00. The deviation of the slope from 1.00 reflected the degree of curvature in the dose-exposure relationship. For AUC_{0-∞}, C_{1h}, and C_{24h}, the geometric means (90% CIs) for the slope were 1.00 (0.97, 1.03), 1.02 (0.99, 1.06), and

Table II Number of Patients With Clinical Adverse Events: Multiple-Dose Administration

	Caspofungin 100 mg (n = 15)			Placebo (n = 5)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Localized infusion site reactions						
Ecchymosis	2					
Erythema	7	1		1		
Induration	4					
Infiltration	1	1	1	1		
Pain at infusion site	5					1
Pruritus	2					
Swelling	4	1				
Tenderness	3	3				
Other clinical adverse events						
Abdominal pain				1		
Constipation	1					
Diarrhea	1					
Dizziness	1			1		
Dry throat				1		
Epistaxis	1					
Flatulence	1					
Headache	3	1	1	2	1	
Rash	1					
Tape allergy	1					
Twitching	1					
Vomiting	1					

0.97 (0.93, 1.02), respectively. This analysis suggested that caspofungin $AUC_{0-\infty}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ were approximately dose proportional over the range of 5 to 210 mg.

Multiple-Dose Study (Part II)

Safety. All 20 participants were included in the safety analyses. Fifteen participants received caspofungin and 5 participants received matching placebo. One participant who received placebo was lost to follow-up and did not have any safety (or pharmacokinetic) evaluations performed after day 22. No serious clinical adverse events were reported, and no participants discontinued the study because of a clinical adverse event. Overall, the most common clinical adverse events were related to tolerability at the infusion site, occurring in 13 of 15 participants who received caspofungin and 3 of 5 participants who received placebo (Table II). Most of these events were mild in intensity. Headache was the most common clinical adverse event not associated with infusion site tolerability, occurring in 5 of 15 participants

who received caspofungin and 3 of 5 participants who received placebo. Drug-related clinical adverse events were reported in 1 participant, a 20-year-old woman with a history of a drug allergy to fluoxetine, and consisted of a mild midsternal rash and mild to moderate pruritus on day 2. These reactions did not require discontinuation from the study and did not recur during the 21-day course of caspofungin. One participant had an elevation in AST that was 2 times the upper limit of normal (ULN) at 84 IU/L (normal range, 10-42 IU/L) and an alanine aminotransferase (ALT) value of 70 IU/L (normal range, 10-60 IU/L) on day 35; these values returned to the normal range by day 49 (39 and 40 IU/L, respectively). Another participant had elevations in AST and ALT that were >2 times but <4 times the ULN. The AST was 66 IU/L and ALT was 118 IU/L on day 16 and day 19, respectively. The participant continued in the study, receiving all 21 days of caspofungin. The highest AST and ALT values (120 and 193 IU/L, respectively) were obtained on day 22 (24 hours after the final dose) and returned to the normal range (34 and 54 IU/L) by days 37 and 44, respectively. Neither

participant had any known concurrent medical conditions that might cause an increase in AST and ALT values. In both participants, the elevations in AST and ALT were classified as probably related to study drug. Four other participants who received caspofungin had slight elevations in AST and/or ALT that were <1.5 times ULN.

Pharmacokinetics. Steady state appears to have been reached by the beginning of the third week of dosing. Mean plasma concentration-time profiles on days 14 and 21 were similar (Figure 3). Figure 4 shows the mean course of trough concentrations at doses from 15 mg to 100 mg daily. Consistent with lower doses studied, in general, the rate of increase in trough concentration was greatest during the first few days of drug administration and appeared to slow thereafter.¹³ The day 21/day 14 GMRs (90% CI) for $AUC_{0-24\text{ h}}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ were 1.04 (1.01, 1.07), 0.97 (0.92, 1.03), and 1.10 (1.05, 1.15). Although these values were statistically greater than 1 for $AUC_{0-24\text{ h}}$ and $C_{24\text{ h}}$ ($P = .050, .002$, respectively), analysis of the least squares change in trough concentration over successive ranges of days indicated a stable plateau by day 15. The change in $C_{24\text{ h}}$ on days 14 to 21 and days 15 to 21 had $P = .056$ and $.800$, respectively. In addition, the degree of accumulation on days 14 and 21 of administration relative to day 1 was similar (GMR [90% CI] day 14/day 1 and day 21/day 1 for the $AUC_{0-24\text{ h}}$ for caspofungin were 1.63 [1.56, 1.69] and 1.69 [1.63, 1.74], respectively; Table III). The time to steady state was dose dependent, with steady state being reached in 3 to 4 days after administration of 15 mg once daily, but not until the third week of drug administration at higher doses (50-100 mg).¹³ Consistent with the dose-dependent nature for the time to steady state, the degree of accumulation also increased with dose (Figure 5). The GMR (day 14/day 1) and 90% CI for the $AUC_{0-24\text{ h}}$ of caspofungin ranged from 1.24 (1.15, 1.33) at 15 mg daily to 1.63 (1.56, 1.69) at 100 mg daily. Similar changes in the degree of accumulation with dose were noted for $C_{1\text{ h}}$ and $C_{24\text{ h}}$. The degree of nonlinearity in the pharmacokinetics of caspofungin was not markedly increased with higher doses, but there was a consistent, modest increase in the degree of nonlinearity over the entire dose range from 15 to 100 mg. A slight upward curvature was observed in the plots of $AUC_{0-24\text{ h}}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$ on day 14 versus dose (Figure 6), indicating slightly greater than dose-proportional increases in multiple-dose pharmacokinetics. The curvature was small enough relative to the pharmacokinetic parameters to indicate that the

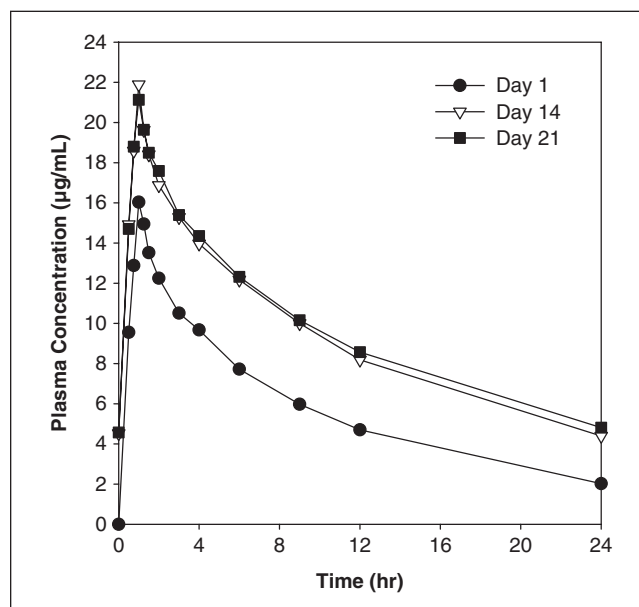


Figure 3. Mean plasma profiles following multiple dosing of caspofungin 100 mg once daily administered as a 1-hour infusion.

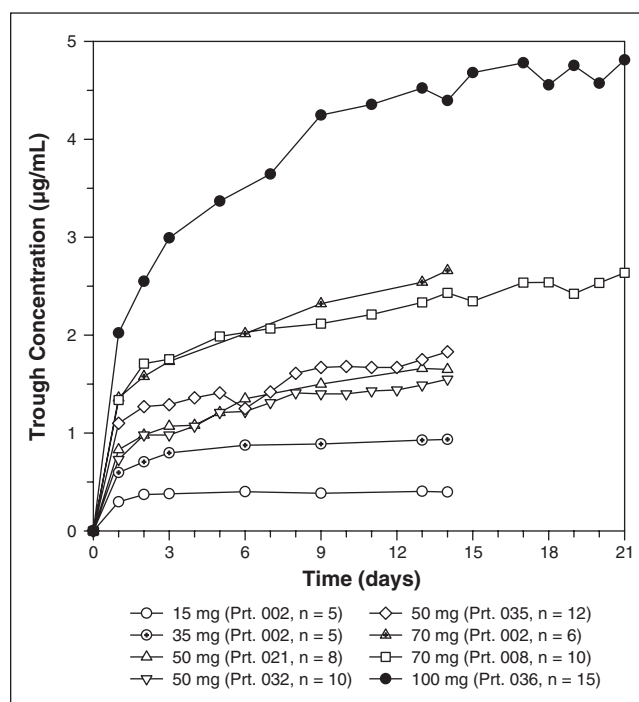


Figure 4. Mean trough concentrations ($\mu\text{g/mL}$) following multiple dosing of caspofungin once daily. From P002 (Multiple-Rising Dose Study in Healthy Subjects), P008 (Multiple-Dose Study With Administration for 3 Weeks), P021 (Multiple-Dose Itraconazole Interaction Study), P032 (Rifampin or Nelfinavir Interaction Study), P035 (Rifampin Interaction Study), and P036 (High-Dose Study With 21 Days of Administration in Healthy Subjects).

Table III Plasma Pharmacokinetic Parameters of Caspofungin After Intravenous Infusion of 100-mg Doses of Caspofungin Once Daily for 21 Days

Pharmacokinetic Parameter	n	Geometric Mean (90% CI)	Accumulation Ratio Relative to Day 1 ^a (90% CI)
AUC _{0-24 h} , µg·h/mL			
Day 1	15	134.7 (126.9, 142.8)	—
Day 14	15	218.9 (201.8, 237.5)	1.63 (1.56, 1.69)
Day 21	15	227.4 (211.1, 244.8)	1.69 (1.63, 1.74)
GMR (90% CI)	15	1.04 (1.01, 1.07)	
C _{1 h} , µg/mL			
Day 1	15	15.9 (14.8, 17.0)	—
Day 14	15	21.5 (19.6, 23.5)	1.35 (1.27, 1.45)
Day 21	15	20.9 (19.3, 22.5)	1.32 (1.25, 1.38)
GMR (90% CI)	15	0.97 (0.92, 1.03)	
C _{24 h} , µg/mL			
Day 1	15	2.0 (1.7, 2.2)	—
Day 14	15	4.3 (3.8, 4.8)	2.18 (2.03, 2.33)
Day 21	15	4.7 (4.2, 5.2)	2.40 (2.26, 2.55)
GMR (90% CI)	15	1.10 (1.05, 1.15)	
β-phase half-life, h	15	12.6 (1.7) ^b	—
γ-phase half-life, h	15	49.4 (4.8) ^b	—

CI, confidence interval; GMR, geometric mean ratio (day 21/day 14).

a. Accumulation ratio calculated as the geometric mean ratio of day 14 or day 21 value over day 1 value.

b. Harmonic mean (jackknife standard deviation) reported for half-life.

nonlinearity probably had little clinical significance over the dose range evaluated. After administration of the last dose of caspofungin on day 21, the harmonic mean β- and γ-phase half-lives of caspofungin were 12.6 hours and 49.4 hours, respectively (Table II). Comparing these data to half-life estimates at lower doses, there was a fairly consistent trend of an increasing harmonic mean β-phase half-life with dose (8.6, 9.5, 10.1, and 10.7-11.2 for 15-, 35-, 50-, and 70-mg daily doses, respectively¹³). In contrast, although the γ-phase half-lives obtained at doses from 15 to 100 mg varied from 40.9 to 50.2 hours, there was no consistent pattern of increasing γ-phase half-life with dose. The accumulation half-life of caspofungin at 100 mg daily, calculated based on the day 21/day 1 accumulation ratio, was ~18 hours.

DISCUSSION

Therapeutic efficacy of anti-infective agents is related to various factors, including mechanism of action, drug concentration relative to the organism sensitivity, duration of treatment, and drug concentration at the site of infection. Caspofungin is used to treat localized or systemic fungal infections. Such infections are especially difficult to treat, a characteristic likely associated with these aforementioned factors, and can often be life threatening. Caspofungin

provides a novel mechanism of action to clinicians for the treatment of fungal infections. However, therapeutic failure still occurs with caspofungin (as well as with other antifungal agents). Higher doses and/or longer duration of treatment with existing agents may provide another therapeutic option for clinicians. Thus, the purpose of the current study was to evaluate the safety, tolerability, and pharmacokinetics after administration of 100-mg doses of caspofungin once daily for 21 days.

The current study shows that administration of caspofungin once daily for 21 days was generally well tolerated. The most common adverse events were local infusion site reactions and headache. Most of the reported adverse events were mild to moderate in intensity and did not result in discontinuation from the study, as was previously observed in phase I studies of ~400 healthy participants who received single or multiple doses of 35 to 70 mg.¹⁵ In the current study, 2 participants experienced pruritic rashes, one after a single 210-mg dose and the other on day 2 of caspofungin 100 mg/d. In the latter case, the participant did not report similar events despite continuation of drug administration for an additional 19 days. In general, the safety and tolerability profile observed in the current study is consistent with that observed in phase II/III safety and efficacy studies, with phlebitis being reported

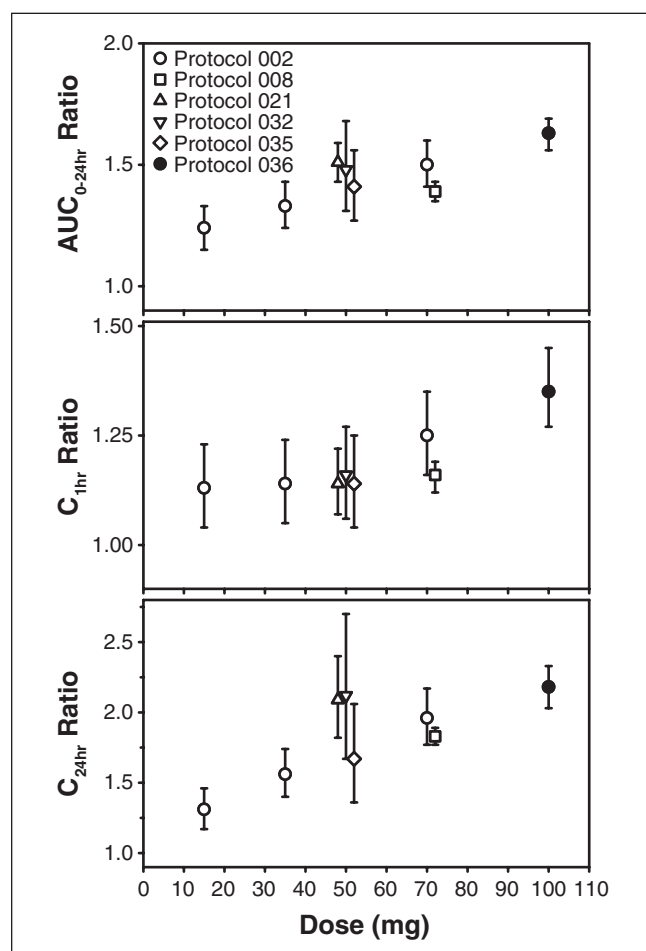


Figure 5. Geometric mean accumulation ratios (day 14/day 1) of AUC_{0-24h} , C_{1h} , and C_{24h} (90% confidence intervals) vs dose following multiple intravenous infusions of caspofungin once daily. Some 50-mg and 70-mg data are slightly offset. P002 (Multiple-Rising Dose Study in Healthy Subjects), P008 (Multiple-Dose Study With Administration for 3 Weeks), P021 (Multiple-Dose Itraconazole Interaction Study), P032 (Rifampin or Nelfinavir Interaction Study), P035 (Rifampin Interaction Study), and P036 (High-Dose Study With 21 Days of Administration in Healthy Subjects).

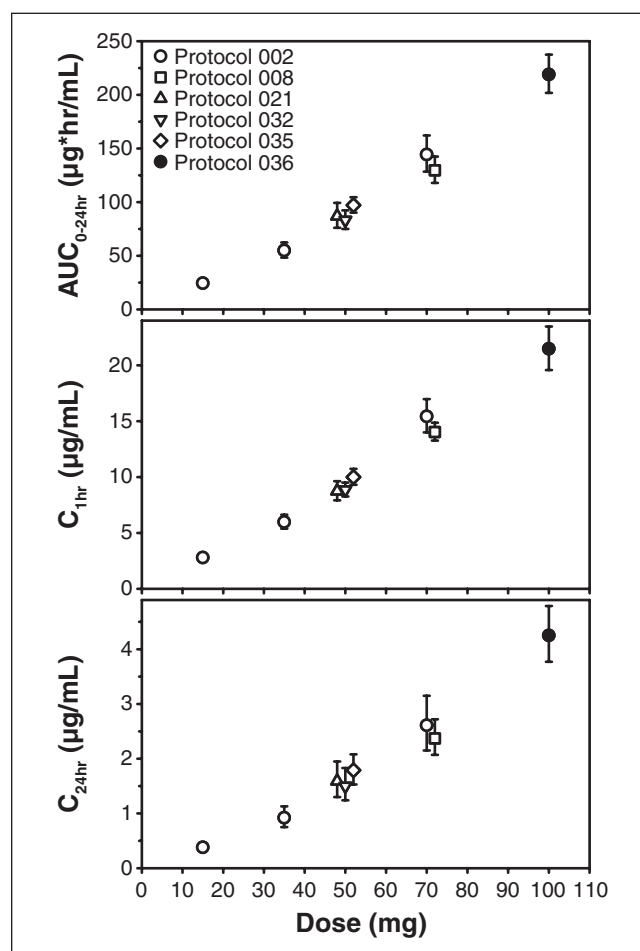


Figure 6. Geometric mean day 14 AUC_{0-24h} , C_{1h} , and C_{24h} (90% confidence intervals) vs dose following multiple intravenous infusions of caspofungin once daily. Some 50-mg and 70-mg data were slightly offset. P002 (Multiple-Rising Dose Study in Healthy Subjects), P008 (Multiple-Dose Study With Administration for 3 Weeks), P021 (Multiple-Dose Itraconazole Interaction Study), P032 (Rifampin or Nelfinavir Interaction Study), P035 (Rifampin Interaction Study), and P036 (High-Dose Study With 21 Days of Administration in Healthy Subjects).

in 12% to 18% of patients (similar to rates observed for fluconazole and amphotericin B), headache in 8% to 12% of patients, and rash in <10% of patients.¹⁵

One participant had an elevation in AST that was 2 times the ULN. Another participant had elevations in AST and ALT >2 times but <4 times the ULN. These elevations were reversible in <1 month in both cases and despite continuation of caspofungin in 1 case. Four participants had elevations in AST and/or ALT that were <1.5 times the ULN during caspofungin administration. In other phase I studies

of caspofungin, elevations in AST and ALT were generally mild (the greatest number of participants had elevations that were >2 but <3 times the baseline value), transient, and reversible and did not appear to be dose related. Hence, administration of higher doses of caspofungin does not appear to increase the risk for hepatic-related effects.

The clearance values of caspofungin at lower doses (historical data) and higher doses (current study) were similar, with a trend toward slightly reduced clearance at the higher doses. At higher doses, plasma drug concentrations declined in a

polyphasic manner after the end of infusion, which was consistent with the profile observed at lower doses, and the β -phase half-lives were similar to estimates previously obtained at lower doses. After multiple-dose administration, drug accumulation was less than 2-fold, consistent with the accumulation at lower doses. Results indicated that steady state was achieved in the third week of drug administration, by as early as day 15, although some participants may not have reached steady state until days 17 to 21 of administration. It is important to point out, however, that the majority (~77%) of drug exposure (AUC) occurs in the beta elimination phase (half-life on the order of 10 hours). A longer γ -phase (half-life on the order of 30-40 hours) becomes apparent at higher doses (when caspofungin plasma concentrations remain above the lower limit of detection for much longer) and is likely responsible for the extended time to reach steady state. This γ -phase accounts for only ~15% of total AUC, so the additional accumulation that occurs in the second and third weeks of dosing is relatively small. The effective half-life of caspofungin at 100 mg daily, calculated based on the day 21/day 1 accumulation ratio, was ~18 hours.

In a linear system, the properties of additivity and scalability hold. As applied to pharmacokinetic parameters, a drug with linear pharmacokinetics would demonstrate plasma drug concentrations that increase proportionally with dose, and upon multiple-dose administration, both the degree of accumulation and the time to steady state would be independent of the dose. In a previous study, after administration of multiple once-daily doses of caspofungin ranging from 15 to 70 mg, both the degree of accumulation and the time to steady state were shown to be dose dependent, which indicated a modest nonlinearity in the pharmacokinetics of caspofungin, with drug accumulation identified as the most sensitive measure of nonlinearity in the pharmacokinetics of caspofungin. To further address whether the degree of nonlinearity in caspofungin pharmacokinetics at 100 mg/d was substantially increased over that observed previously at lower doses, the pharmacokinetics of caspofungin in the current study were compared with historical data. The pharmacokinetics on day 14 and the accumulation ratios (day 14/day 1) were used for this comparison because most of the historical data were from 14-day studies. Although steady state was achieved only after 14 days of administration at higher doses, the accumulation after day 14 was

slight, so comparison with day 14 data in earlier studies was reasonable.

Analysis of the pharmacokinetic parameters of caspofungin after multiple-dose administration in this study suggested some nonlinearity at higher doses, with a greater than dose-proportional increase in $AUC_{0-24\text{ h}}$, $C_{1\text{ h}}$, and $C_{24\text{ h}}$. The mechanism of the pharmacokinetic (PK) nonlinearity after multiple dosing is unclear. The nonlinearity may be associated with the gamma distribution phase, as this phase was not well characterized for single doses below ~70 mg. Therefore, the apparent PK linearity observed following single doses may not necessarily reflect linearity of the γ -phase. Caspofungin disposition is thought to be primarily determined by OATP1B1-mediated uptake into hepatocytes and chemical (spontaneous) degradation.¹⁶ There is no reason to expect the chemical degradation to exhibit nonlinearity, but it is possible that a slight saturation in the uptake process could result in the modest PK nonlinearity observed. However, the deviations from dose proportionality are slight and not considered to be clinically meaningful. For comparison, caspofungin 150 mg once daily has been well tolerated in patients with invasive candidiasis.¹⁷

In conclusion, the results of this study suggest that caspofungin 100 mg given once daily for up to 21 days is generally safe and well tolerated and displays a pharmacokinetic profile consistent with that observed at lower doses.

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REFERENCES

1. Ernst EJ, Klepser ME, Ernst ME, Messer SA, Pfaller MA. In vitro pharmacodynamic properties of MK-0991 determined by time-kill methods. *Diagn Microbiol Infect Dis.* 1999;33:75-80.
2. Antachopoulos C, Meletiadis J, Sein T, Roilides E, Walsh TJ. Concentration-dependent effects of caspofungin on the metabolic activity of *Aspergillus* species. *Antimicrob Agents Chemother.* 2007;51:881-887.
3. Abruzzo GK, Gill CJ, Flattery AM, et al. Efficacy of the echinocandin caspofungin against disseminated aspergillosis and candidiasis in cyclophosphamide-induced immunosuppressed mice. *Antimicrob Agents Chemother.* 2000;44:2310-2318.

4. Lewis RE, Albert ND, Kontoyiannis DP. Comparison of the dose-dependent activity and paradoxical effect of caspofungin and micafungin in a neutropenic murine model of invasive pulmonary aspergillosis. *J Antimicrob Chemother.* 2008;61:1140-1144.
5. Villaneuva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med.* 2002;113:294-299.
6. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med.* 2002;347:2020-2029.
7. Cornely OA, Lasso M, Betts R, et al. Caspofungin for the treatment of less common forms of invasive candidiasis. *J Antimicrob Chemother.* 2007;60:363-369.
8. Walsh TJ, Teppner H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 2004;351:1391-1402.
9. Maertens J, Raad I, Petrikos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis.* 2004;39:1563-1571.
10. CANCIDAS® (caspofungin acetate) for injection [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; 2005. http://www.merck.com/product/usa/pi_circulars/c/cancidas/cancidas_pi.pdf
11. Safdar A, Rodriguez G, Rolston KVI, et al. High-dose caspofungin combination antifungal therapy in patients with hematologic malignancies and hematopoietic stem cell transplantation. *Bone Marrow Transpl.* 2007;39:157-164.
12. Schwartz M, Kline W, Matuszewski B. Determination of a cyclic hexapeptide (L-743872), a novel pneumocandin antifungal agent in human plasma and urine by high-performance liquid chromatography with fluorescence detection. *Analytica Chimica Acta.* 1997;352:299-307.
13. Stone JA, Holland SD, Wickersham PJ, et al. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agents Chemother.* 2002;46:739-745.
14. Stone JA, Migoya EM, Hickey L, et al. Potential for drug interactions between caspofungin and nelfinavir or rifampin. *Antimicrob Agents Chemother.* 2004;48:4306-4314.
15. Sable CA, Nguyen B-YT, Chodakewitz JA, DiNubile MJ. Safety and tolerability of caspofungin acetate in the treatment of fungal infections. *Transpl Infect Dis.* 2002;4:25-30.
16. Stone JA, Xu X, Winchell GA, et al. Disposition of caspofungin: role of distribution in determining pharmacokinetics in plasma. *Antimicrob Agents Chemother.* 2004;48:815-823.
17. Betts R, Nucci M, Talwar D, et al. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. *Clin Infect Dis.* 2009;48:1676-1684.

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