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Potential for Interactions between Caspofungin and Nelfinavir or Rifampin

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The potential for interactions between caspofungin and nelfinavir or rifampin was evaluated in two parallel-panel studies. In study A, healthy subjects received a 14-day course of caspofungin alone (50 mg administered intravenously [IV] once daily) ($n = 10$) or with nelfinavir (1,250 mg administered orally twice daily) ($n = 9$) or rifampin (600 mg administered orally once daily) ($n = 10$). In study B, 14 subjects received a 28-day course of rifampin (600 mg administered orally once daily), with caspofungin (50 mg administered IV once daily) coadministered on the last 14 days, and 12 subjects received a 14-day course of caspofungin alone (50 mg administered IV once daily). The coadministration/administration alone geometric mean ratio for the caspofungin area under the time-concentration profile calculated for the 24-h period following dosing [$AUC_{0–24}$] was as follows (values in parentheses are 90% confidence intervals [CIs]): 1.08 (0.93–1.26) for nelfinavir, 1.12 (0.97–1.30) for rifampin (study A), and 1.01 (0.91–1.11) for rifampin (study B). The shape of the caspofungin plasma profile was altered by rifampin, resulting in a 14 to 31% reduction in the trough concentration at 24 h after dosing (C_{24h}), consistent with a net induction effect at steady state. Both the AUC and the C_{24h} were elevated in the initial days of rifampin coadministration in study A (61 and 170% elevations, respectively, on day 1) but not in study B, consistent with transient net inhibition prior to full induction. The coadministration/administration alone geometric mean ratio for the rifampin $AUC_{0–24}$ on day 14 was 1.07 (90% CI, 0.83–1.38). Nelfinavir does not meaningfully alter caspofungin pharmacokinetics. Rifampin both inhibits and induces caspofungin disposition, resulting in a reduced C_{24h} at steady state. An increase in the caspofungin dose to 70 mg, administered daily, should be considered when the drug is coadministered with rifampin.

Caspofungin (known by the trade name CANCIDAS; also known as MK-0991) is a parenteral antifungal agent that inhibits 1,3-β-D-glucan synthesis, which forms a critical component of the cell wall of many fungal species (3). Caspofungin is active against many clinically important fungal species, including *Candida* spp. and *Aspergillus* spp. (2, 4, 8, 15). In clinical trials, it has been shown to be efficacious in the treatment of esophageal candidiasis (1, 16, 17), invasive candidiasis (9), and invasive aspergillosis (J. Maertens, I. Raad, G. Petrikkos, D. Selleslag, F. Petersen, C. Sable, N. Kartsonis, A. Ngai, A. Taylor, T. Patterson, D. Denning, and T. Walsh, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-868, 2002). Caspofungin is approved for the treatment of invasive aspergillosis in patients refractory to or intolerant of standard therapy, invasive candidiasis, and esophageal candidiasis.

Metabolism and excretion of caspofungin are very slow processes (13). In contrast to the situation with many other drugs, neither of these processes is the rate-controlling step that determines the clearance of caspofungin from plasma. Rather, plasma clearance is determined primarily by the rate of distribution of caspofungin from plasma into hepatocytes and possibly other tissue cells (13). The uptake of caspofungin into tissue cells appears to be mediated, at least in part, by an active transport process (13).

This paper describes results from two phase I studies of healthy subjects conducted to evaluate the potential for nelfinavir, a human immunodeficiency virus protease inhibitor, or rifampin, an RNA polymerase inhibitor active against tuberculosis and other bacteria, to alter the pharmacokinetics of caspofungin. These studies were undertaken because a drug-interaction screening analysis using population pharmacokinetic data from patients with esophageal and/or oropharyngeal candidiasis had indicated that the use of inducers of drug clearance or nelfinavir might result in clinically meaningful reductions in the caspofungin area under the time-concentration profile (AUC) and trough concentration at 24 h postdosing (C_{24h}) (J. Stone, S. Li, G. Winchell, S. Bi, P. Wickersham, M. Schwartz, N. Kartsonis, and C. Sable, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1571, 2003). Additionally, it is reasonable to expect that these drugs will be used in combination at times in clinical practice. Immunocompromised people are susceptible to developing active tuberculosis, as well as invasive fungal infections. Patients with AIDS may develop fungal infections due to their immunocompromised state.

Rifampin was chosen as a model inducer to test the hypothesis that inducers could alter caspofungin pharmacokinetics, since it is a potent inducer that affects a broad spectrum of

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drug-disposition processes. These phase I studies provide a more definitive evaluation of the potential for drug interactions with nelfinavir or rifampin than could be obtained with population pharmacokinetics data in view of their prospective study designs, the larger numbers of subjects receiving the combinations, more extensive pharmacokinetics evaluation, exclusion of other concomitant therapies, and the lack of major underlying illnesses in participating subjects.

MATERIALS AND METHODS

Study A. Study A was an open-label, randomized, parallel-panel study of healthy male subjects to investigate the potential for nelfinavir and rifampin to alter the pharmacokinetics of caspofungin. Subjects received one of three treatment regimens in which drugs were administered daily over 14 days, as follows: panel 1, 50 mg of caspofungin administered intravenously (IV) once daily (n = 10); panel 2, 50 mg of caspofungin administered IV once daily and 600 mg of rifampin administered orally once daily (n = 10); and panel 3, 50 mg of caspofungin administered IV once daily and 1,250 mg of nelfinavir administered orally every 12 h (n = 9). IV doses of caspofungin were administered as a constant-rate infusion over 1 h. Subjects in each panel ingested a fixed moderate-fat meal prior to dosing. Rifampin and the morning dose of nelfinavir were administered just prior to the start of the caspofungin infusion on coadministration days. Subjects enrolled in this study (and the second study described below) were male, nonsmokers in generally good health, who had no history of drug or alcohol abuse and who did not take prescription medications, St. John's wort, or other herbal remedies within 14 days or nonprescription medications or grapefruit products within 7 days of the start of the study. Blood samples were drawn and plasma was collected for assay at 0 (predose) and 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, and 24 h after dosing on days 1 and 14. To obtain intervening trough (24-h postdose) concentrations, blood samples were also drawn just prior to dosing on days 2 to 13. The 29 healthy men enrolled had an average age of 31 years (range, 18–44), an average weight of 76 kg (range, 62–93), and the following racial distribution: 14 white subjects, 12 black subjects, 2 Hispanic subjects, and 1 multiracial subject.

Study B. This was an open-label, randomized, parallel-panel study of healthy male subjects to further investigate the potential for interactions between caspofungin and rifampin. Subjects received one of two treatment regimens, as follows: panel 1, 50 mg of caspofungin administered IV once daily for 14 days (n = 12); and panel 2, 600 mg of rifampin administered orally once daily for 28 days, with 50 mg of caspofungin coadministered IV once daily for the final 14 days (n = 14). IV doses of caspofungin were administered as a constant-rate infusion over 1 h. Subjects in each panel ingested a fixed moderate-fat meal prior to dosing. Rifampin was administered just prior to the start of the caspofungin infusion on coadministration days. To characterize caspofungin pharmacokinetics, blood samples were drawn and plasma was collected for assay at 0 (predose) and 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, and 24 h after dosing on days 1 and 14 of caspofungin dosing; blood samples (to obtain intervening trough concentrations) were also drawn just prior to dosing on days 2 to 13. For panel 2, plasma samples were collected at 0 (predose) and 1, 2, 4, 6, 9, 12, and 24 h after dosing on day 14 (prior to coadministration of caspofungin), day 15 (day 1 of coadministration), and day 28 (day 14 of coadministration) of rifampin dosing to characterize rifampin pharmacokinetics. The 26 healthy men enrolled had an average age of 35 years (range, 18–44), an average weight of 76 kg (range, 58–92), and the following racial distribution: 4 white subjects, 3 black subjects, and 19 Hispanic subjects.

The study protocols described in this report were approved by the Institutional Review Board of Thomas Jefferson University (study A) or by the Southern Institutional Review Board of Miami, Florida (study B), and informed consent was obtained from all subjects.

Bioanalytical analysis. Plasma samples for determination of caspofungin concentrations were stored at [minus]70°C until analysis. Plasma concentrations of caspofungin were determined by high-pressure liquid chromatography (HPLC) with fluorescence detection as previously described (11). 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. The standard curve range was 125 to 10,000 ng/ml in the modified assay. The intraday precision of the assay, as measured by the percent coefficient of variation (%CV) of the peak height ratios, was better (i.e., less) than 10% (1.2 to 9.4%) at all points of the standard line. The interday variability of the assay, as assessed by the %CV of the quality control samples, ranged from 3.3 to 6.4%. In addition, a column-switching procedure was employed as described in reference 12. No interference of rifampin with the caspofungin assay was seen.

Plasma samples were analyzed for the presence of rifampin by MDS Pharma Services, Sunnyvale, Calif., using HPLC with ultraviolet light detection. Approximately 1 mg of ascorbic acid/ml was added to all plasma samples for the rifampin assay prior to freezing for improved stability. Rifampin and the internal standard, papaverine, were extracted from buffered plasma with chloroform. After evaporation and reconstitution, the extract was injected onto a C_{18} HPLC column and the rifampin was measured by absorbance at 340 nm. The limit of quantitation was 0.1 μg/ml. The standard curve range was 0.1 to 25 μg/ml. The intraday precision of the assay, as measured by the %CV, was better than 10% (3.8 to 8.9%) at all points of the standard line. The interday variability of the assay, as assessed by the %CV of the quality control samples, ranged from 5.7 to 10.8%. No interference of caspofungin with the rifampin assay was seen.

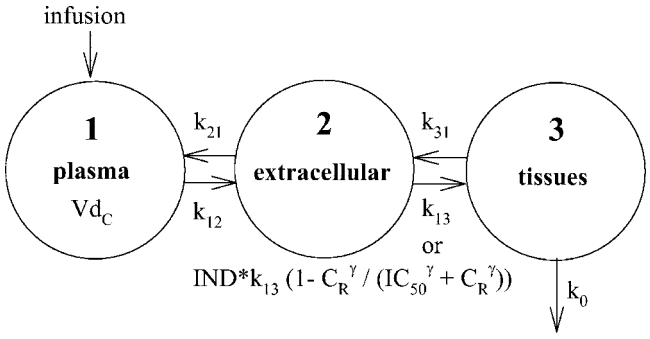

FIG. 1. Schematic of compartmental model to describe the effect of rifampin on caspofungin pharmacokinetics.

Pharmacokinetic analysis. The AUC over the 24-h interval following dosing [AUC_{0-24}] was calculated by the linear-log trapezoidal method. Actual sampling times, as recorded by the investigator, were used for calculation of the AUC_{0-24}. For several caspofungin concentration-time profiles, the timing of the end of infusion and the C_{1h} plasma sampling differed by more than 1 min, and in one instance the C_{1h} plasma sample was not obtained. In these instances, an estimated end-of-infusion concentration, determined by fitting the plasma concentration time data to a three-compartment linear model, was used along with the plasma concentration data in the AUC calculations. For rifampin plasma profiles, the maximum concentration of drug in serum (C_{max}) and time to maximum concentration of drug in serum (T_{max}) were determined by inspection.

A pharmacokinetic model of the effect of rifampin on caspofungin pharmacokinetics was developed (Fig. 1). Caspofungin pharmacokinetics were represented by a three-compartment model with elimination from the third compartment. This model structure is consistent with disposition data which indicate that uptake of caspofungin into tissues is the primary mechanism controlling plasma pharmacokinetics and that the elimination processes (metabolism and excretion) are slow and appear to occur largely subsequent to the tissue uptake process (13). In the model, both the induction and inhibition effects of rifampin on caspofungin pharmacokinetics act on the tissue uptake rate constant (k_{13}). The induction process is modeled by a scaling factor, IND, which represents the fold increase in intrinsic k_{13} at maximal (steady-state) induction. The inhibition effect is modeled as a function of rifampin concentration (C_{RIF}) using a Hill function $1 - C_{RIF}^{\gamma}/(IC_{50}^{\gamma} + C_{RIF}^{\gamma})$, where IC_{50} is the 50% inhibitory concentration and the superscript γ is the sigmoidicity.

The differential equations that compose the caspofungin model are as follows:

$$\frac{dA_1}{dt} = IR + k_{21} \cdot A_2 - k_{12} \cdot A_1 \quad (1)$$

$$\frac{dA_2}{dt} = k_{12} \cdot A_1 - k_{21} \cdot A_2 + k_{31} \cdot A_3 - IND \cdot k_{13} \cdot \left(1 - \frac{C_{RIF}^{\gamma}}{IC_{50}^{\gamma} + C_{RIF}^{\gamma}}\right) \cdot A_2 \quad (2)$$

$$\frac{dA_3}{dt} = IND \cdot k_{13} \cdot \left(1 - \frac{C_{RIF}^{\gamma}}{IC_{50}^{\gamma} + C_{RIF}^{\gamma}}\right) \cdot A_2 - k_{31} \cdot A_3 - k_0 \cdot A_3 \quad (3)$$

where A denotes amount; the subscripts 1, 2, and 3 denote the central, extracellular fluid, and tissue compartments, respectively; k_{12}, k_{21}, k_{13}, and k_{31} are the microconstants defining transfer between the compartments; k_0 is the elimination rate constant; and IR is the infusion rate (IND, IC_{50}, and γ are as described above). The measured concentrations in plasma are related to A_1 by the central volume of distribution (V_C).

Several variations on this model were considered during model development,

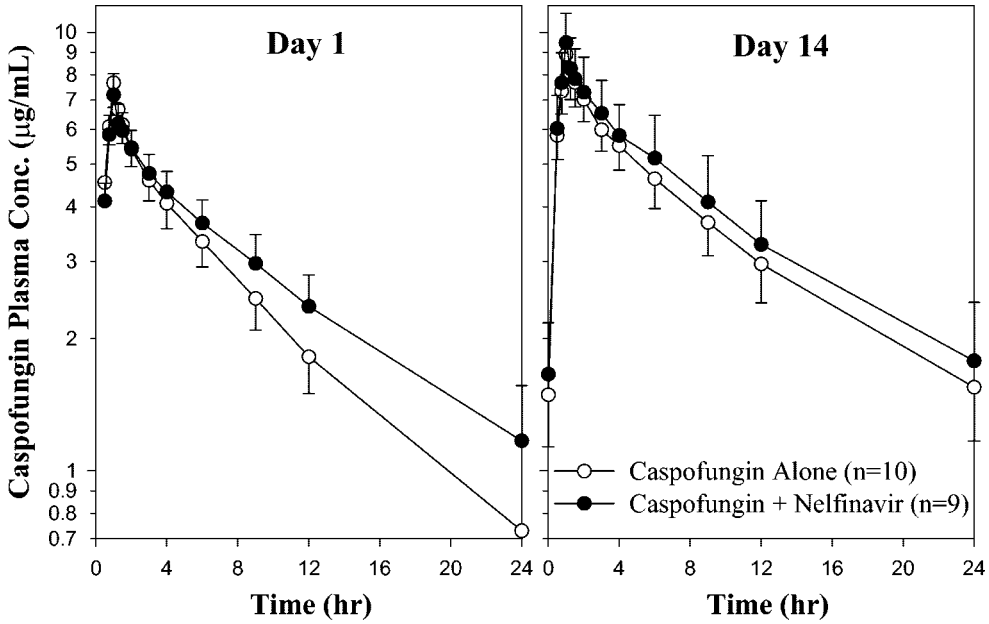

FIG. 2. Caspofungin plasma profiles following administration of caspofungin alone (50 mg administered IV once daily) or coadministration of caspofungin (as described above) and nelfinavir (1,250 mg administered orally twice daily) to healthy male subjects. Means and standard deviations (error bars) are indicated. Conc., concentration.

including addition of a rifampin link model which allowed rifampin concentrations in an effect compartment to lag behind plasma rifampin concentrations. This addition did not improve the model fit to data, and the fit values obtained did not suggest a time delay between plasma concentrations and effective concentrations. A second model variation evaluated involved allowing induction and inhibition by rifampin to act only on a fraction of k_{13}, with the remaining fraction unaffected by rifampin. Model fits to data with this variation estimated the fraction of k_{13} affected by rifampin to be ~100%, so this addition also was not included in the final model.

The software package ACSL (Aegis Software, Huntsville, Ala.) was used for the modeling analysis. The model parameters were fit to weighted ($1/y^2$, where y is the magnitude of the concentration) caspofungin plasma data by maximization of the log-likelihood function using a generalized reduced gradient search algorithm. Because the model did not allow for variation in the induction factor (IND) with time, the model was only fit to data obtained under either no induction (IND = 1.0), i.e., caspofungin monotherapy or day 1 of rifampin administration, or stable maximal induction, i.e., day 28 of rifampin administration in study B. First, the model was fit to study B data, i.e., panel 1 (caspofungin monotherapy) data on all study days and panel 2 (caspofungin plus rifampin) data on day 14 of coadministration. Rifampin plasma concentrations on all days of coadministration were obtained by linear interpolation of the individual day 28 rifampin concentration data. Second, the model was fit to the day 1 data from study A, with IND set to 1.0 for both monotherapy and combination therapy. Because no rifampin plasma concentration data were available for study A, rifampin concentrations for this fit were obtained by linear interpolation of the mean rifampin profile concentrations obtained in study B. Because the study A data fit was limited to day 1, it was not possible to estimate all the parameters for the underlying caspofungin model. Therefore, k_0 and k_{31} were set to the values obtained in the fit-to-study-B data. For both data sets, the model was fit to the pooled set of individual profile data from combination and monotherapy panels to obtained mean parameter estimates. Therefore, no estimates of intersubject dispersion in the mean parameter values were obtained. This was necessary, since any given individual had only combination or monotherapy data available due to the parallel-panel design of these studies. In addition to the parameter estimates, standard deviations characterizing the estimation precisions were determined for each fit using established routines in the ACSL software program.

Statistical analysis. All subjects who completed the pharmacokinetics sampling for a study were included in the pharmacokinetics analysis. Unless otherwise noted, all tests were two-sided and assumed a significance level of 0.05.

To evaluate the effect of rifampin (studies A and B) or nelfinavir (study A) on caspofungin pharmacokinetics, a between-panel comparison of the natural log-transformed pharmacokinetics data [AUC_{0-24}, C_{1h}, and C_{24h}] was conducted based upon a one-way analysis of variance model with treatment as a factor. The observed differences in means and limits of the corresponding 90% confidence intervals (CIs) were exponentiated to obtain the geometric mean ratios (coadministration/administration alone) and the corresponding 90% CIs.

To evaluate the effect of caspofungin on rifampin pharmacokinetics in study B, a within-group comparison of the natural log-transformed AUC and C_{max} from panel 2 was conducted. Mean differences and the corresponding 90% CIs were exponentiated to obtain geometric mean ratios (coadministration/administration alone) and 90% CIs. In order to assess the effect on the rifampin T_{max}, the Hodges-Lehmann estimate of median difference and the corresponding 90% CIs were calculated.

RESULTS

Effect of nelfinavir on caspofungin pharmacokinetics. The effect of coadministration of nelfinavir on the pharmacokinetics of caspofungin was evaluated in study A. A modest difference in the concentration-time profiles of caspofungin was seen on day 1, with a shallower decline in caspofungin plasma concentrations evident between 4 h and 24 h after dosing in the presence of nelfinavir (Fig. 2). On day 14, little difference was observed in the plasma concentration profiles from the two panels. Alterations in caspofungin pharmacokinetics with nelfinavir were at most modest (Table 1). There were statistically significant elevations in AUC ($P = 0.022$) and C_{24h} ($P = 0.001$) of 16 and 58%, respectively, on day 1. After approximately day 2, the trough concentrations climbed more slowly in the nelfinavir combination panel than in the control panel, such that, on day 14, there were no statistically significant differences in any of the pharmacokinetics parameters in subjects receiving caspofungin alone and in combination with nelfinavir.

Effect of rifampin on caspofungin pharmacokinetics. The effect of coadministration of rifampin on the pharmacokinetics of caspofungin was evaluated in both studies A and B. In both studies, parallel panels received 14 days of caspofungin alone or of caspofungin coadministered with rifampin. The primary difference between the two study designs was in the timing of

TABLE 1. Effect of nelfinavir on the pharmacokinetics of caspofungin (study A)[a]

Day and caspofungin PK parameter	Caspofungin coadministered with nelfinavir		Caspofungin administered alone		Geometric mean ratio (90% CI)[b]
	n	Geometric mean	*n*	Geometric mean	
Day 1					
AUC_{0-24} (μg · h/ml)	9	65.14	10	56.07	1.16 (1.05–1.29)
C_{1h} (μg/ml)	9	7.15	10	7.61	0.94 (0.86–1.02)
C_{24h} (μg/ml)	9	1.12	10	0.71	1.58 (1.28–1.94)
Day 14					
AUC_{0-24} (μg · h/ml)	9	89.85	10	83.17	1.08 (0.93–1.26)
C_{1h} (μg/ml)	9	9.34	10	8.86	1.05 (0.95–1.17)
C_{24h} (μg/ml)	9	1.70	10	1.50	1.13 (0.85–1.50)

[a] Nelfinavir (1,250 mg) was administered orally twice daily, and caspofungin (50 mg) was administered IV once daily. PK, pharmacokinetics.
[b] Caspofungin plus nelfinavir/caspofungin alone.

the initiation of the rifampin therapy. In study A, rifampin and caspofungin were initiated on the same study day. In study B, rifampin was administered alone for 14 days prior to coadministration with caspofungin.

Mean plasma concentration-time profiles on days 1 and 14 of caspofungin therapy in subjects receiving caspofungin alone and in combination with rifampin are shown in Fig. 3 (study A) and 4 (study B). When caspofungin and rifampin were initiated on the same day (study A), there were statistically significant ($P < 0.001$) elevations in AUC_{0-24} and C_{24h} of 61 and 170%, respectively, on day 1, but not day 14, in the panel receiving caspofungin with rifampin compared to the panel receiving caspofungin alone (Table 2). The caspofungin trough concentration data provide insight into the time course of this transient elevation in plasma caspofungin concentrations with rifampin. Caspofungin trough concentrations in the rifampin combination panel of study A reached an arithmetic mean peak of 2.49 μg/ml on day 2 (Fig. 5). After day 2, the trough concentrations fell throughout the remainder of the study.

The mean plasma profile of caspofungin obtained on day 14 in the rifampin combination panel was somewhat different in shape from the one obtained for the control panel (Fig. 3). There was a noticeable shoulder around 6 to 9 h after dosing in the profile obtained with rifampin, indicating that caspofungin clearance is reduced by rifampin early in the dosing interval. Plasma concentrations in the interval 12 to 24 h after dosing appeared to fall faster in the combination panel than in controls, indicating that caspofungin clearance was increased by rifampin later in the dosing interval. Consistent with the alteration in the profile shape observed, there is a trend towards a slight reduction in trough concentration on day 14 with rifampin in study A. On day 1, the shoulder from 6 to 9 h after dosing was also prominent in the group receiving rifampin, but no subsequent accelerated decline was observed during the 12- to 24-h postdose interval. This pattern suggests that only reduced caspofungin clearance is present on the first day of dosing with rifampin.

It was unclear from the study A data whether further reductions in caspofungin concentrations would be observed following more than 14 days of rifampin treatment. In study B, rifampin alone was administered for 14 days prior to coadministration in order to ensure that the induction effect reached steady state during the coadministration period.

When a 14-day pretreatment with rifampin alone was given

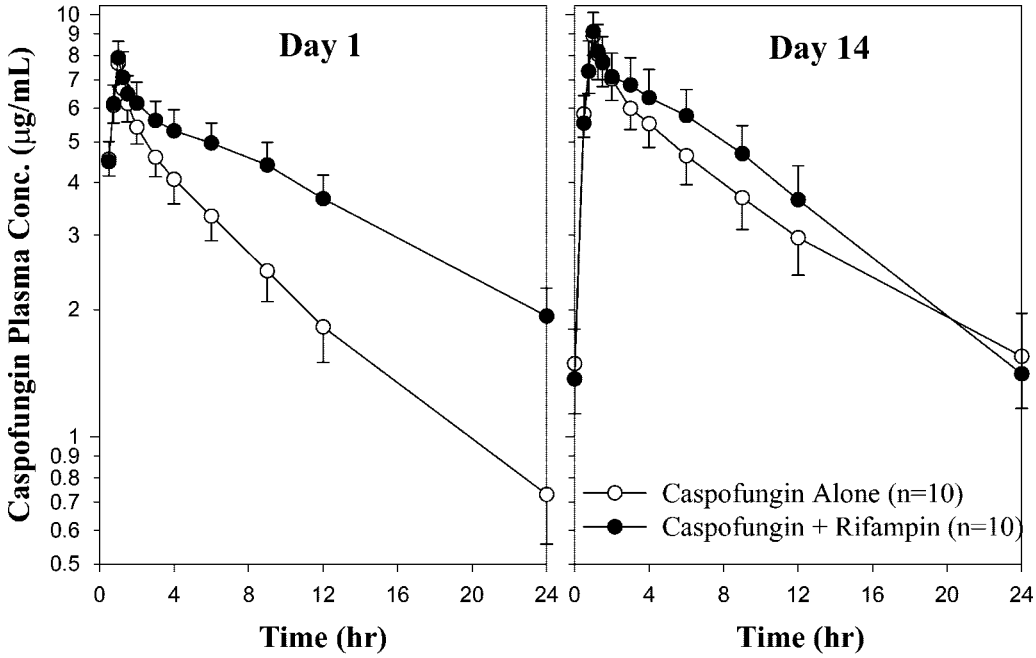

FIG. 3. Caspofungin plasma profiles following administration of caspofungin alone (50 mg administered IV once daily) or coadministration of caspofungin (as described above) and rifampin (600 mg administered orally once daily) when both drugs were initiated on the same study day (study A). Means and standard deviations (error bars) are indicated. Conc., concentration.

TABLE 2. Effect of rifampin on the pharmacokinetics of caspofungin[a]

Study, day, and caspofungin PK parameter	Caspofungin coadministered with rifampin		Caspofungin administered alone		Geometric mean ratio (90% CI)[b]
	n	Geometric mean	*n*	Geometric mean	
Study A					
Day 1					
AUC_{0-24} (μg · h/mL)	10	90.44	10	56.07	1.61 (1.46, 1.79)
C_{1h} (μg/ml)	10	7.87	10	7.61	1.03 (0.95, 1.12)
C_{24h} (μg/ml)	10	1.91	10	0.71	2.70 (2.20, 3.31)
Day 14					
AUC_{0-24} (μg · h/ml)	10	93.35	10	83.17	1.12 (0.97, 1.30)
C_{1h} (μg/ml)	9[c]	9.05	10	8.86	1.02 (0.92, 1.13)
C_{24h} (μg/ml)	10	1.30	10	1.50	0.86 (0.65, 1.14)
Study B					
Day 1					
AUC_{0-24} (μg · h/ml)	14	75.08	12	69.05	1.09 (0.99, 1.20)
C_{1h} (μg/ml)	14	8.43	12	8.76	0.96 (0.89, 1.04)
C_{24h} (μg/ml)	14	0.76	12	1.07	0.71 (0.58, 0.87)
Day 14					
AUC_{0-24} (μg · h/ml)	14	97.89	12	97.14	1.01 (0.91, 1.11)
C_{1h} (μg/ml)	14	9.61	12	10.00	0.96 (0.87, 1.06)
C_{24h} (μg/ml)	14	1.24	12	1.79	0.69 (0.56, 0.85)

[a] Rifampin (600 mg) was administered orally once daily, and caspofungin (50 mg) was administered IV once daily. PK, pharmacokinetics.
[b] Caspofungin plus rifampin/caspofungin alone.
[c] No C_{1h} sample was obtained for one subject.

prior to coadministration (study B), there were no statistically significant alterations in the caspofungin AUC_{0-24} or C_{1h} on days 1 or 14 with coadministration of rifampin. The mean caspofungin plasma profiles obtained on days 1 and 14 in the rifampin combination panel of study B had an alteration similar to that observed on day 14 in study A (Fig. 3 and 4), including a noticeable shoulder around the 6- to 9-h postdose interval and an accelerated decline in the 12- to 24-h postdose interval. Consistent with the alteration in the profile shape observed, statistically significant reductions of 29% ($P = 0.007$) and 31% ($P = 0.006$) in caspofungin trough concentration with coadministration of rifampin were observed on days 1 and 14, respectively, in study B. The time course of trough concentrations indicates that the reduced trough concentrations with rifampin are maintained throughout the 14 days of coadministration, when the pretreatment with rifampin alone was given prior to coadministration (Fig. 5).

Effect of caspofungin on rifampin pharmacokinetics. The effect of coadministration of caspofungin on the pharmacokinetics of rifampin was investigated in study B. Mean plasma concentration-time profiles for rifampin from panel 2 subjects receiving rifampin alone (day 14 of rifampin alone) and in combination with caspofungin (days 1 and 14 of coadministration) are shown in Fig. 6. Table 3 summarizes the effect of caspofungin on the pharmacokinetics of rifampin. There were no statistically significant differences in the rifampin AUC_{0-24} or C_{max} on day 1 or 14 of coadministration relative to day 14 of administration of rifampin alone. The T_{max} was similar on the 3 days that the profiles were evaluated.

Modeling analysis of pharmacokinetic interaction between caspofungin and rifampin. A pharmacokinetic modeling analysis was used to explore whether a combination of inhibitory and induction effects could account for the changes in the

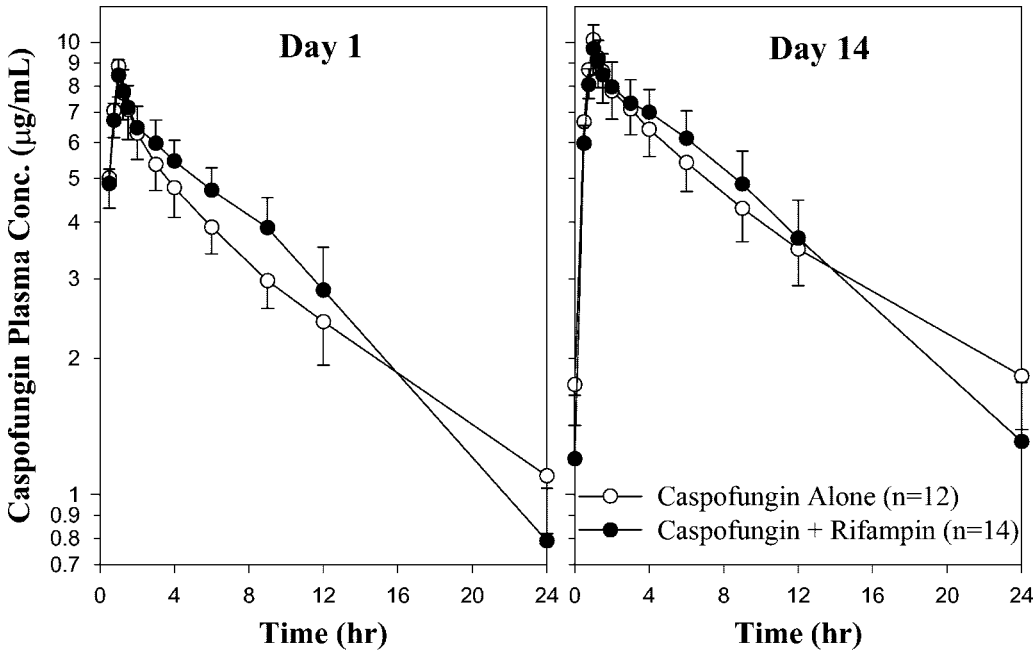

FIG. 4. Caspofungin plasma profiles following administration of caspofungin alone (50 mg administered IV once daily) or coadministration of caspofingin (as described above) and rifampin (600 mg administered orally once daily) when rifampin was initiated alone 14 days prior to coadministration with caspofungin (study B). Means and standard deviations (error bars) are indicated. Conc., concentration.

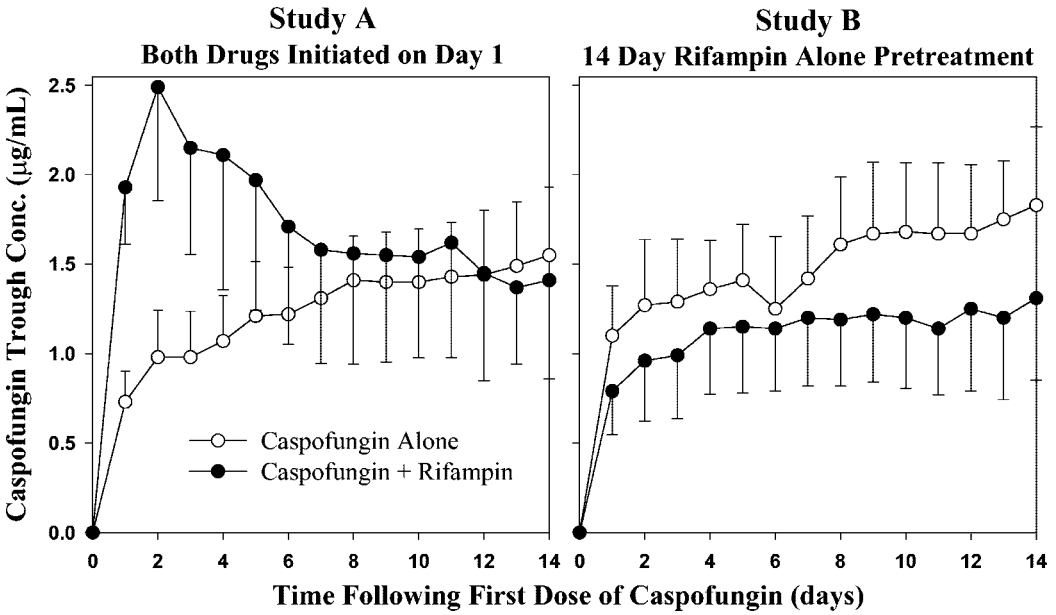

FIG. 5. Caspofungin trough concentrations following administration of caspofungin alone (50 mg administered IV once daily) or coadministration of caspofungin (as described above) and rifampin (600 mg administered orally once daily). Means and standard deviations (error bars) are indicated. Conc., concentration.

shape of the caspofungin plasma profile that were observed with coadministration of rifampin. Figure 7 illustrates the model fit to caspofungin plasma concentration data from day 1 of study A and day 14 of study B. The day 14 data were well represented by the model incorporating both inhibitory and induction effects, including accounting for the shoulder in the combination profile at 6 to 9 h after dosing and the accelerated decline in the 12- to 24-h postdose interval. Similarly, the day 1 data from study A were well represented by the model with the induction factor (IND) set to 1.0 (no induction) for both combination and monotherapy, including accounting for the shoulder in the combination profile at 6 to 9 h after dosing and the continued elevation in the combination profile through 24 h after dosing. Table 4 provides the parameter estimates obtained from fitting the model to the data sets. The parameter estimates are reasonably consistent across both sets of data evaluated.

DISCUSSION

The results of these studies indicate that rifampin has both an inhibitory and an induction effect on caspofungin disposition, with a net effect of slight induction at steady state. In study A, coadministration of rifampin with caspofungin resulted in a transient increase in caspofungin concentrations on day 1. The results are consistent with net inhibition of caspofungin disposition in the initial days of concomitant administration when rifampin therapy is initiated at the same time as caspofungin therapy. The effect's being evident on day 1 during the β distribution phase of caspofungin suggests that rifampin inhibits the uptake of caspofungin into tissues. Previous results from a single-dose disposition study of [^{3}H]caspofungin (13) indicate that little metabolism or excretion occur during the first 24 h after dosing and that uptake of drug into tissues is the mechanism controlling the decline of drug concentration observed during the dominant β phase evident from approximately 6 to 48 h after dosing.

By day 14 in study A and on both days 1 and 14 in study B, the caspofungin AUC and end-of-infusion concentrations in the combination panel were similar to those obtained with controls. However, an alteration in the shape of the caspofun-

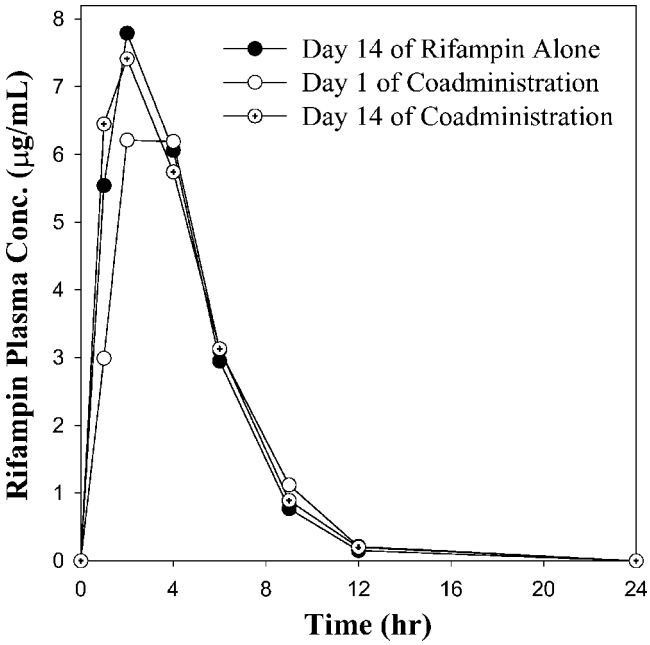

FIG. 6. Rifampin plasma profiles following administration of rifampin alone (600 mg administered orally once daily) or coadministration of rifampin (as described above) and caspofungin (50 mg administered IV once daily) (n = 14). Data are means. Conc., concentration.

TABLE 3. Effect of caspofungin on the pharmacokinetics of rifampin (study B)[a]

Rifampin PK parameter	Geometric mean on[b]:			Geometric mean ratio (90% CI)	
	Day 14	Day 15	Day 28	(1st day of coadministration/control)	(14th day of coadministration/control)
AUC_{0-24} (μg · h/ml)	35.25	33.44	37.75	0.95 (0.80–1.13)	1.07 (0.83–1.38)
C_{max} (μg/ml)	8.86	8.35	8.67	0.94 (0.79–1.13)	0.98 (0.78–1.23)
T_{max} (h)[c]	2.00	2.00	2.00	0.50 (−1.5–2.5)	0.00 (−2.0–2.0)

[a] Data are from study B, panel 2 (n = 14). Caspofungin (50 mg) was administered IV once daily, and rifampin (600 mg) was administered orally once daily. PK, pharmacokinetics.
[b] Day 14 data are for controls who received rifampin alone. Day 15 was the first day the drugs were coadministered, and day 28 was the 14th day the drugs were coadministered.
[c] For T_{max}, the "geometric means" are median values and the "mean ratios" are median differences (coadministration versus control), with 95% CI provided.

gin plasma concentration profile with rifampin coadministration resulted in a 14 to 31% reduction in caspofungin trough concentrations relative to controls on those study days. The declining trough concentrations observed with continued concomitant dosing with rifampin in study A are consistent with induction of a caspofungin disposition process. The results from study B, including the reduced caspofungin trough concentrations throughout the coadministration period, are also consistent with induction of caspofungin disposition by rifampin, since the pretreatment with rifampin alone allowed substantial induction of this disposition process to occur prior to the start of coadministration.

The caspofungin tissue uptake mechanism controlling the decline in plasma concentrations in the β phase, presumably the mechanism inhibited by rifampin, is unknown. Rifampin has recently been shown to inhibit the rat uptake transporters Oatp1 and Oatp2 (5, 14), but it is not known if either of these transporters is involved in the disposition of caspofungin. The same uptake mechanism inhibited by rifampin in the initial days of therapy may also be induced by rifampin with continued dosing. It is not unreasonable to postulate that rifampin could induce uptake transporters, since rifampin induces a number of metabolic pathways and has recently been shown to induce the efflux transporter P-glycoprotein (6, 7). Induction of caspofungin metabolism is unlikely to be the mechanism generating these pharmacokinetic alterations with longer-term rifampin administration. Uptake of caspofungin into tissues is the rate-controlling step for plasma clearance of caspofungin and the initial biotransformation process appears to be chemical decomposition (13). Therefore, induction of metabolic pathways would be expected to have little, if any, effect on caspofungin plasma pharmacokinetics.

The modeling analysis suggests that a combination of induction and inhibition effects of rifampin on caspofungin tissue uptake can account for the caspofungin plasma profile alterations observed. The parameter estimates obtained suggest that induction by rifampin roughly doubles the rate of caspofungin uptake into tissues, although the presence of ongoing inhibition by rifampin results in more-modest alterations in the plasma pharmacokinetics of caspofungin. In general, the model represented the concentration data well. On both day 1 and day 14, the model appeared to underpredict the degree of inhibition at 2 to 4 h after dosing. A possible explanation for this is that rifampin plasma concentrations may underrepre-

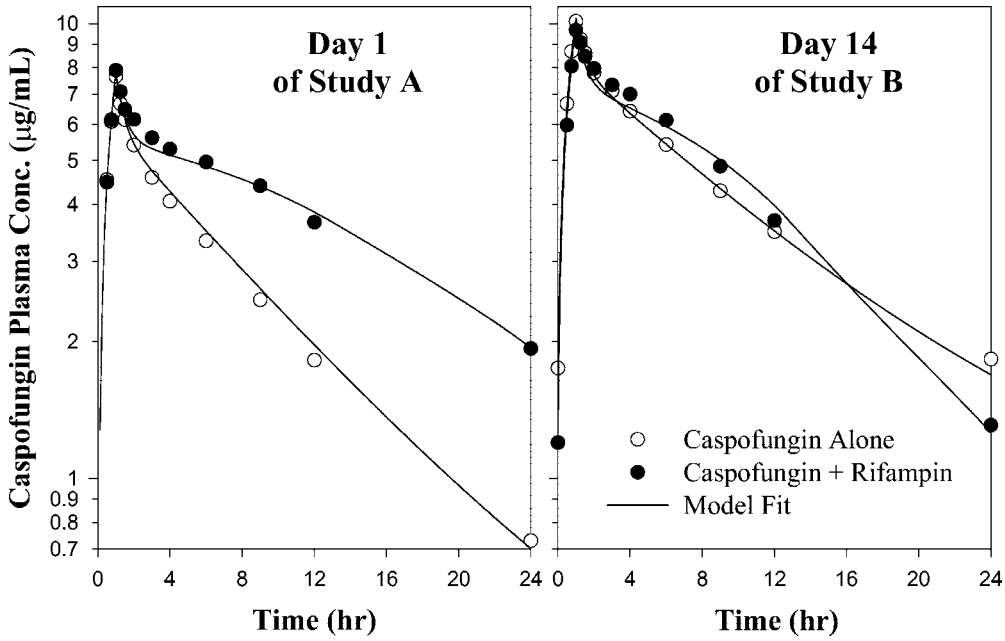

FIG. 7. Mean model fit to caspofungin concentration data from day 1 of coadministration in study A (caspofungin and rifampin initiated on same day) and from day 14 of coadministration in study B (pretreatment with rifampin alone). Conc., concentration.

TABLE 4. Model parameter estimates from fit of three-compartment, linear models with caspofungin uptake into tissue compartment induced and inhibited by rifampin

Parameter[a]	Estimate (precision SD)	
	Fit to study B data	Fit to study A data
k_0 (h^{-1})	0.0156 (NA[d])	0.0156[b]
k_{12} (h^{-1})	0.993 (0.004)	1.00 (0.05)
k_{13} (h^{-1})	0.191 (0.003)	0.216 (0.011)
K_2	1.04 (0.002)	1.03 (0.05)
K_3	0.0222 (0.0001)	0.0222[b]
V_C (l)	4.12 (0.03)	4.60 (0.04)
IC_{50} (μg/ml)	0.411 (0.001)	0.270 (0.075)
γ	0.372 (0.004)	0.334 (0.099)
IND	2.16 (0.01)	—[c]

[a] $K_2 = k_{21}/k_{12}$; $K_3 = k_{31}/k_{13}$.
[b] For fit of study A data, parameter set to value from study B fit.
[c] —, for fit of study A data, IND was set to 1.0 (no induction).
[d] NA, not available.

sent hepatic concentrations during the rifampin absorption phase and, thus, the model may not fully account for the degree of inhibition of caspofungin uptake into hepatocytes during this period.

Caspofungin trough concentrations were reduced by 14 to 31% following multiple doses of rifampin. The clinical significance of this alteration is unclear. In a dose-ranging study conducted in patients with esophageal and oropharyngeal candidiasis, patients treated with 35 mg of caspofungin had a numerically lower favorable response rate than patients treated with doses of 50 or 70 mg of caspofungin, although this difference was not statistically significant (1). The caspofungin dose of 35 mg produced trough concentrations that were ~70% of the value obtained with 50 mg in the efficacy study described above (J. Stone et al., 43rd ICAAC). Although the critical caspofungin pharmacokinetic parameter (AUC, peak, or trough) for efficacy is unknown, the response data at 35 mg indicate a possibility that a trough reduction of 30% or more may be associated with reduced efficacy. In patients with proven or potentially life-threatening fungal infections, caution indicates that dosing decisions should err on the side of ensuring that effective drug concentrations are achieved. The 90% CIs for the geometric mean ratios (coadministration/administration alone) of caspofungin trough concentrations fell below 0.7 on day 14 of study A and on days 1 and 14 of study B, indicating that the reduction in caspofungin trough concentrations with coadministered rifampin may be clinically meaningful. Therefore, an increase in the daily maintenance dose of caspofungin from 50 to 70 mg should be considered when caspofungin and rifampin are coadministered. This dose increase should generate trough concentrations similar to those obtained when 50-mg doses of caspofungin are given without concomitant rifampin. While this dose increase would also increase the AUC_{0-24} and C_{1h}, these parameter values should be similar to or only slightly in excess of those obtained with 70-mg doses of caspofungin given daily without rifampin. The 70-mg/day regimen has been generally well tolerated in clinical studies (10, 12).

Administration of rifampin with caspofungin produces a transient elevation in caspofungin plasma concentrations on day 1 of coadministration when both drugs are initiated together, but not when caspofungin is added after administration of rifampin for the preceding 14 days. A dose reduction is not considered to be necessary for the transient elevation in caspofungin plasma concentrations when rifampin and caspofungin are initiated on the same study day. The geometric mean caspofungin AUC_{0-24} of 90.44 μg · h/ml obtained in the coadministration panel on day 1 in study A is similar to the AUC_{0-24} values that were obtained with acceptable tolerability following a single 100-mg dose (113.92 μg · h/ml) and following multiple doses of 70 mg (129.61 to 144.27 μg · h/ml) (12) and is much less than values obtained with acceptable tolerability following single doses of 150 and 210 mg (279.66 and 374.92 μg · h/ml, respectively) and multiple doses of 100 mg (227.36 μg · h/ml) (J. Stone, E. Migoya, S. Li, P. Deutsch, G. Winchell, K. Ghosh, A. Miller, S. Bi, A. Bass, G. Mistry, and R. Dawkins, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstract A-1389, 2002). Therefore, it is unlikely that this transient elevation would be clinically meaningful. In addition, these transient elevations will occur only under conditions where rifampin is initiated at the same time or after caspofungin is initiated. Under typical clinical usage, it is more likely that caspofungin will be added to preexisting rifampin therapy, and under these conditions, no transient elevation will occur, as verified in study B.

The effect of caspofungin on the pharmacokinetics of rifampin was also investigated in study B. A comparison of rifampin pharmacokinetics on the final day of pretreatment with rifampin alone and on days 1 and 14 of coadministration indicates that caspofungin has no effect on the pharmacokinetics of rifampin.

Finally, the results from study A also provide information on concomitant use of nelfinavir. Caspofungin pharmacokinetics on day 14 were unaltered by coadministration of nelfinavir. Although a slight elevation in caspofungin concentrations was noted on day 1 of coadministration, this alteration is unlikely to be clinically meaningful. Given that this study provides a more definitive evaluation of the potential for drug interactions with nelfinavir than could be obtained with population pharmacokinetic data, the lack of clinically meaningful alterations in caspofungin pharmacokinetics indicates that no dose adjustment is necessary when caspofungin and nelfinavir are administered together. It also suggests that the association of a reduced AUC and trough concentration with concomitant use of nelfinavir in the prior analysis of the population pharmacokinetics data was a spurious finding.

In conclusion, nelfinavir has no clinically significant effect on the pharmacokinetics of caspofungin. No dose adjustment is necessary when caspofungin is coadministered with nelfinavir. Caspofungin has no effect on the pharmacokinetics of rifampin. Rifampin both inhibits and induces caspofungin disposition, resulting in reduced trough concentrations at steady state. An increase in the caspofungin dose to 70 mg daily should be considered when the drug is coadministered with rifampin.

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