# Single- and Multiple-Dose Administration of Caspofungin in Patients With Hepatic Insufficiency: Implications for Safety and Dosing Recommendations

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*This report investigated safety and dosing recommendations of intravenous caspofungin in hepatic insufficiency. In the single-dose study, 8 patients each with mild and moderate hepatic insufficiency received 70 mg of caspofungin. In the multiple-dose study, 8 patients with mild hepatic insufficiency and 13 healthy matched controls received 70 mg on day 1 and 50 mg daily on days 2 through 14. Eight patients with moderate hepatic insufficiency received 70 mg on day 1 and 35 mg daily on days 2 through 14. Caspofungin was generally well tolerated with no discontinuations due to serious or nonserious adverse experiences. The area under the concentration–time profile over the interval of last quantifiable point to infinity ($AUC_{0-\infty}$) geometric mean ratio (GMR) (90% confidence interval [CI]) for mild hepatic insufficiency/historical controls was 1.55 (1.32-1.86) in the single-dose study and for mild hepatic insufficiency/concurrent controls was 1.21 (1.04-1.39) for day 14 area under the concentration–time profile calculated over the interval 0 to 24 hours ($AUC_{0-24h}$) following multidose. The $AUC_{0-\infty}$ GMR (90% CI) for moderate hepatic insufficiency/historical controls was 1.76 (1.51-2.06) following 70 mg; $AUC_{0-24h}$ GMR (90% CI) for moderate hepatic insufficiency/concurrent controls was 1.07 (0.90-1.28) on day 14 after 35 mg daily. No dosage adjustment is recommended for patients with mild hepatic insufficiency. A dosage reduction to 35 mg daily following the 70-mg loading dose is recommended for patients with moderate hepatic insufficiency.*

***Keywords:*** *MK-0991; caspofungin; pharmacokinetics; hepatic insufficiency*

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Caspofungin acetate is first in a novel class of antifungal drugs known as the enchinocandins and was initially prescribed for the parenteral treatment of invasive aspergillosis in patients who were refractory to or intolerant to existing therapies.[1,2] More recently, the indication for caspofungin has been broadened to include invasive candidiasis,[3] esophageal candidiasis,[4-6] and empirical therapy in febrile neutropenic patients.[7] The duration of therapy in phase II/III clinical studies with caspofungin was approximately 7 to 14 days.[8] The recommended clinical dose for treating confirmed or suspected invasive fungal infections with caspofungin is a 70-mg loading dose followed by a once-daily maintenance dose of 50 mg infused over 1 hour.[1]

The most common drug-related clinical adverse experiences associated with the use of the 35-, 50-, and 70-mg doses of caspofungin in patients enrolled

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in clinical studies were fever and infusion site reactions (phlebitis), which were reported in 12% to 26% and 12% to 18% of the patients, respectively.[8] Laboratory adverse experiences commonly associated with the use of caspofungin at the above-mentioned doses include increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). ALT elevations occurred in 11% to 24% of the patients, and increases in AST and ALP typically increased in concert with ALT levels.[8] Caspofungin has a half-life of 9 to 10 hours, with low renal clearance of unchanged drug of 10 to 12 mL/min.[9] Metabolism and excretion of caspofungin are very slow processes.[10] In contrast to many drugs, neither of these processes is the rate-controlling step that determines the clearance of caspofungin from plasma. Rather, the plasma clearance is determined primarily by the rate of distribution of caspofungin from plasma into hepatocytes and possibly other tissue cells.[10] The uptake of caspofungin into tissue cells appears to be mediated, at least in part, by an active transport process.[10,11] It was unclear before conducting this study what effect hepatic insufficiency (HI) might have on this uptake transport process.

This report describes the results of 2 phase I studies, single and multiple dose, conducted primarily in patients with varying degrees of HI. These studies examined the effect of mild to moderate HI (1 patient with severe HI) on the pharmacokinetics of caspofungin after single- and multiple-dose administration. The studies also assessed the safety and tolerability of caspofungin following single- and multiple-dose administration in patients with varying degrees of HI. The results from the 2 studies provide justification for the dose recommendations for patients with mild or moderate HI given in the product circular.

## METHODS

The single- and multiple-dose studies were conducted according to the provisions of the Declaration of Helsinki, and written informed consent was obtained from each study participant before conducting any study-related procedures. Both studies were conducted by Clinical Pharmacology Associates and approved by the Southern Institutional Review Board in Miami, Florida.

A total of 17 subjects, 12 males and 5 females, in the single-dose study and 29 subjects, 21 males and 8 females, in the multiple-dose study, at least 18 years of age, were enrolled. In the single-dose study, 8 patients with mild, 8 patients with moderate, and 1 patient with severe HI participated. In the multiple-dose study, the same number of patients with mild and moderate HI as in the single-dose study were enrolled as well as 13 matched controlled healthy subjects. Patients with HI were required to have a chronic (>6 months) and stable diagnosis with no acute episodes of illness attributable to deterioration in hepatic function within 2 months before receiving administration of caspofungin and with clinical features of liver cirrhosis attributable to any etiology. Aside from HI, the patients were considered to be in otherwise generally good health without other medical conditions or significant abnormalities on the basis of medical history, physical examination including vital signs, 12-lead electrocardiogram (ECG), and laboratory safety tests (hematology, blood chemistry, urinalysis) that were also conducted for the healthy control subjects (historical or matched). In addition, patients with HI were prohibited from taking prescription or nonprescription medications that may interfere with the results of the study. The healthy control subjects and HI patients were nonsmokers and were not permitted to take prescription or nonprescription drugs for 2 weeks before the start of dosing, throughout the study, and for at least 2 weeks after the last dose of study drug without consulting the investigator. The healthy control subjects were in good health based on the clinical evaluations given above. Subjects judged by the investigator to not have clinically significant abnormalities in laboratory tests were allowed in the study. Liver function test results (ALT, AST, alkaline phosphatase, total and direct bilirubin) needed to be within normal range for study participation, although 1 subject with a slightly elevated ALT at predose was allowed in the study because it was judged to be not clinically significant by the investigator (see safety results) and was considered to be an appropriate match for the hepatically impaired subjects. Female subjects, if not surgically sterile or postmenopausal, used double-barrier contraceptive methods (diaphragm and condom [by the partner], intrauterine device and condom, sponge and condom, or spermicide and condom); hormonal therapies, including Depo-Provera, Norplant, and oral contraceptives, were not permitted to avoid potential drug interactions.

The Child-Pugh classification system[12] for the determination of the degree of HI was used to categorize the patients into mild, moderate, or severe HI as follows: mild HI (Child-Pugh score of 5-6), moderate HI (Child-Pugh score of 7-9), severe HI (Child-Pugh score >9). In the multiple-dose study, the healthy subjects were each matched to a patient with HI based on age (±5 years), gender, and weight

(±15%). Healthy subjects were enrolled as needed to identify a matching cohort for the mild HI panel and the moderate HI panel. Thus, the cohort of matched control subjects for patients with moderate HI may have included healthy subjects who had been recruited to match patients with mild HI; that is, 1 healthy subject may have served as a control for a mild HI and a moderate HI patient, both of whom had the same matching demographic characteristics compared with the healthy control subject.

**Study Designs**

The single-dose study was an open-label study where a single 70-mg intravenous (IV) dose of caspofungin was administered on day 1 to patients with mild, moderate, or severe HI. Blood samples for the determination of plasma caspofungin concentrations were collected for 2 weeks postdose, and safety was evaluated for up to 4 weeks postdose. The multiple-dose study was also an open-label study where caspofungin was administered once daily for 14 days to patients with mild or moderate HI and healthy controls. All caspofungin IV doses were administered as a constant-rate infusion over 1 hour. Patients with mild HI and healthy age-, weight-, and gender-matched control subjects received an IV loading dose of 70 mg of caspofungin on day 1 followed by a 50-mg IV dose once daily on days 2 to 14. Patients with moderate HI received the same 70-mg loading dose but then a reduced maintenance 35-mg IV dose once daily on days 2 to 14. Blood samples for the determination of caspofungin plasma concentrations were collected during the 2 weeks of dosing through to 10 days after the day 14 dose, and safety was evaluated for at least 6 weeks after the first dose of caspofungin was administered. To ensure compliance with dosing and to assess safety before discharge after the completion of dosing, all study participants were required to remain in the clinical research unit from the day before the start of dosing through day 2, 24 hours after the completion of dosing for the single-dose protocol, and through day 16, 48 hours after the completion of dosing for the multiple-dose protocol. Drug administration was conducted by the medical staff at the clinical research unit in both studies with no compliance issues being reported.

In the single-dose study, blood samples were collected at 0 hours (predose) and 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, 24, 48, 72, 129, 168, 240, and 336 hours postdose for the determination of plasma caspofungin concentrations. In the multiple-dose study, blood samples were obtained at 0, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours postdose from the start of caspofungin infusion on days 1, 7, and 14 to determine the plasma concentrations of caspofungin. In addition, trough concentrations were determined on days 2, 3, 4, 5, 9, 10, 11, and 12 of drug administration and also were collected following the day 14 (final) dose at 48, 72, 120, and 192 hours postdose.

Safety and tolerability were evaluated in both studies by physical examinations, vital sign measurements, 12-lead ECGs, laboratory safety tests (hematology, blood chemistry, urinalysis), and adverse experience monitoring. In the single-dose study, liver function tests (ALT, AST, ALP, direct and total bilirubin) were measured before and after drug administration on day 1 as well as on days 5, 7, 10, and 28 or 29 postdose while participants were off drug. In the multiple-dose study, liver function test results were obtained on days 1, 2, 4, 6, 10, and 12 during daily administration of caspofungin as well as on days 15, 17, 19, 21, 24, and 42 while participants were off study drug. Furthermore, the study participants provided written consent to allow the investigator, at his discretion, to conduct additional safety tests as needed to follow up on any abnormalities in safety parameters and until values returned to baseline.

**Analytical Methods**

Plasma samples were stored at –70°C until analysis. Plasma concentrations of caspofungin were determined by high-pressure liquid chromatography with fluorescence detection as previously described.[13] The plasma assay was modified slightly to allow for smaller sample volumes; 0.5 mL of plasma was used, with a resulting limit of quantitation of 25 ng/mL. The standard curve range was 25 to 2000 ng/mL in the modified assay. In addition, for the multiple-dose study, a column-switching procedure was used as previously described.[9] In the single-dose study, samples of reconstituted IV solution were analyzed to determine caspofungin concentrations in the infusate.

**Pharmacokinetic Methods**

For the single-dose profiles and the day 14 profile following multiple doses, the plasma terminal rate constants β and γ were calculated by weighted ($1/y^2$) nonlinear regression of individual terminal plasma concentration data using a monoexponential or biexponential decay function. The onset of the log-linear phase was determined visually for each subject. Onset of the β phase generally occurred at 6 to 9 hours postdose. Half-lives ($t_{1/2}$ β and $t_{1/2}$ γ) were

computed as the quotient of ln(2) and the rate constant. Gamma (γ) phase half-lives obtained from the single-dose profiles are not included in the results because they could not be estimated with adequate precision because of the limited data above the quantitation limit.

Area under the concentration–time profile (AUC) was calculated over the interval 0 to last quantifiable point or 24 hours ($AUC_{0\text{-}24h}$) for the multiple-dose study by the linear-log trapezoidal method. For the single-dose study, the AUC over the interval of last quantifiable point to infinity ($AUC_{0\text{-}\infty}$) was extrapolated as the quotient of the last quantifiable concentration and the terminal rate constant. Clearance was determined as the quotient of dose and $AUC_{0\text{-}\infty}$. Actual sampling times, as recorded in the case report forms, were used for calculation of AUC and rate constant. For some of the concentration–time profiles, the end of infusion did not coincide precisely with the actual sampling time for concentration at 1 hour from the start of drug infusion ($C_{1h}$). In these instances, an estimated end of infusion concentration, determined by fitting the plasma concentration–time data to a 3-compartment linear model, was used along with the plasma concentration data in the AUC calculations.

For the single-dose administration, the actual dose administered was calculated as the product of the infusate concentration and net weight administered divided by 1.01 (specific gravity). The concentration-based pharmacokinetic parameters, AUC, $C_{1h}$, and $C_{24h}$, were adjusted to a 70-mg dose equivalent using the ratio of 70 over the administered dose.

### Statistical Analyses

For both studies, a confidence interval (CI) approach was used to determine the clinical significance of any pharmacokinetic alteration in drug response when comparing patients with HI to healthy subjects. In particular, this approach was used to determine whether the true geometric mean ratio (GMR) (HI patient/healthy subject) of the plasma pharmacokinetic parameter $AUC_{0\text{-}\infty}$ fell within the hypothesized interval of (0.7-1.5). A log transformation was first applied to the AUC data. Because of a modest effect of age on the $AUC_{0\text{-}\infty}$ of caspofungin, young and elderly adults were included in the historical control group in order to address the confounding of age and hepatic function. All elderly and young adult subjects of normal hepatic function from a single-dose study[14] were combined with young adult controls from the initial single-dose study.[9] An analysis of variance (ANOVA) model on log-transformed $AUC_{0\text{-}\infty}$ was performed containing a factor for hepatic function with 3 levels (normal, mild, and moderate). Comparisons of severe HI patients to normal controls were not performed because only 1 patient with severe HI was enrolled in the single-dose study. Age was included in the model as a continuous covariate by assuming a linear relationship between age and the effect that it might have on caspofungin pharmacokinetics. From this model, the differences in least-squares means between HI patients and normal controls (and the corresponding 90% CI) were then exponentiated to obtain the 90% CI for the GMR in the test of the primary hypothesis.

In the multiple-dose study, $AUC_{0\text{-}24h}$ data were transformed to the log scale before analysis. The standard error used to construct the 90% CI for the mean difference on log scale (mild to normal) was obtained from an analysis of covariance model that included hepatic function (mild, normal) as the fixed effect factor and age, weight, and gender as covariates in the model. Then the limits of the CI on the log scale were exponentiated to obtain the 90% CI for the GMR. The same statistical method was used to assess the proposed dose reduction for moderate HI, which would be supported if the 2-sided 90% CI for the geometric mean $AUC_{0\text{-}24h}$ ratio of caspofungin following the last dose on day 14 in patients with moderate HI relative to the last dose on day 14 in healthy matched subjects (moderate/normal) was contained in (0.7-1.5).

In the single-dose study, harmonic means (jackknife standard deviation) were reported for β-phase $t_{½}$.

## RESULTS

### Single-Dose Study

*Safety results.* A single 70-mg dose of caspofungin was generally well tolerated by patients with mild and moderate HI. Six of the 17 patients in the study had a total of 12 nonserious, clinical adverse experiences, of which 11 were considered possibly drug related by the investigator. All of the nonserious adverse experiences were mild in intensity. No patient discontinued the study because of an adverse experience. Headache in 3 patients and swelling at the site of infusion of less than or equal to 1-hour duration in 3 patients were the most common nonserious adverse experiences that were considered possibly drug related by the investigator. The reports of headache and swelling were consistent with a grade I toxicity rating attributable to their mild intensities.

Two patients had serious adverse experiences that were not considered to be drug related. One patient with moderate HI was hospitalized for stomach pain attributed to pancreatitis and cholelithiasis, 14 days after receiving a single 70-mg IV dose of caspofungin, which was surgically treated by performing a cholecystectomy. These adverse experiences were considered probably not drug related by the investigator. This patient also had an elevated amylase level that was considered serious because it was attributed to the pancreatitis. The laboratory adverse experience was considered probably not drug related by the investigator. The second patient with a serious adverse experience was the 1 patient with severe HI. This patient was hospitalized for worsening ascites with shortness of breath, 4 days after receiving a single 70-mg IV dose of caspofungin. The ascites was surgically treated by performing a paracentesis. These adverse experiences were considered to be definitely not drug related by the investigator. Both patients recovered from the serious adverse experiences.

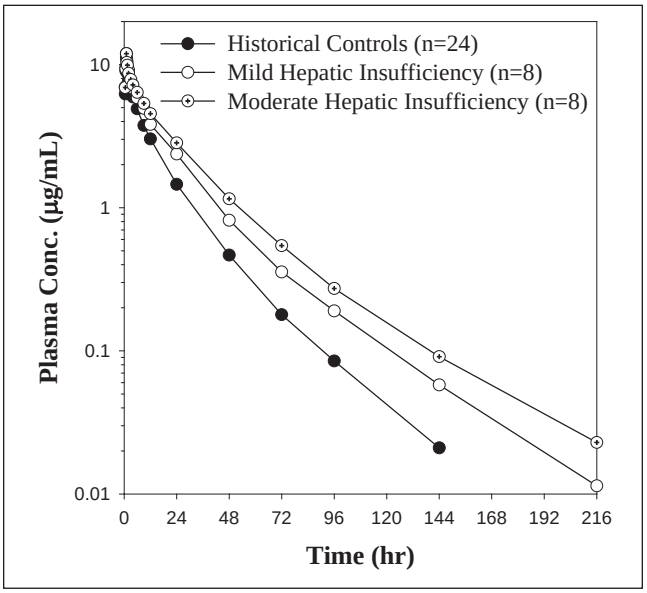


*Figure 1. Mean plasma concentration–time profiles in mild and moderate hepatic insufficiency patients and healthy subjects administered single 70-mg doses of caspofungin.*

*Pharmacokinetic results*. The mean plasma concentration–time profiles obtained from patients with mild and moderate HI and comparisons with healthy historical control subjects are given in Figure 1. Figure 1 clearly illustrates that the plasma concentrations of caspofungin were affected by the degree of HI. Patients with moderate HI tended to have higher plasma concentrations of caspofungin compared with patients with mild hepatic insufficiency and healthy control subjects. At the later time points, the mean concentrations for mild HI patients were intermediate between the moderate HI patients and the healthy control subjects.

For the single-dose study, the initial pharmacokinetic comparison evaluated the pooled mild to moderate HI patients versus the historical healthy control group. The geometric mean $AUC_{0-\infty}$ was 196.89 µg·h/mL for the patients with HI and 119.37 µg·h/mL for the healthy controls. The geometric mean AUC ratio (90% CI) for HI subjects relative to healthy controls was 1.65 (1.46-1.86). The AUC of caspofungin was significantly different between patients of mild or moderate HI and historical controls ($P < .001$), and therefore, comparisons focused on separate analyses based on the degree of HI. The ANOVA model adjusted for the effect of age on $AUC_{0-\infty}$ was also significant ($P = .016$).

Pharmacokinetic parameters for caspofungin are listed in Table I. There was a trend for patients with mild and moderate HI to have increased $AUC_{0-\infty}$, $C_{24h}$, and β-phase half-life relative to healthy historical control subjects. The extent of systemic exposure of caspofungin had increased 55% and 76% in mild and moderate HI patients, respectively, compared with the historical control subjects. A trend of decreasing clearance with an increase in the degree of HI was also evident. Consistent with a decrease in clearance, the half-life of caspofungin increased in patients with mild and moderate HI compared with healthy control subjects.

In the single-dose study, it was not possible to evaluate the effect of severe HI on the pharmacokinetics of caspofungin because only 1 patient was enrolled. This patient had an acute episode of ascites that required draining of peritoneal fluid during the pharmacokinetic sampling period, which confounded any interpretation.

**Multiple-Dose Study**

*Safety results*. Multiple doses of caspofungin were generally well tolerated by patients with mild and moderate HI as well as by healthy subjects. No patient or subject discontinued the study because of an adverse experience, and no patient or subject had a serious adverse experience during multiple dosing with caspofungin, although 1 patient did have a serious adverse experience several days after the final dose of caspofungin (see below). Twenty of the 29

**Table I** Caspofungin Pharmacokinetics in Patients With Mild and Moderate Hepatic Insufficiency Administered Single 70-mg Doses

| Pharmacokinetic Parameters[a] | Historical Controls (n = 24) | Mild HI (n = 8) | Moderate HI (n = 8) | GMR (90% CI) Mild HI/Control | GMR (90% CI) Moderate HI/Control |
|---|---|---|---|---|---|
| $AUC_{0-\infty}$, μg·h/mL | 119.37 | 184.45 | 210.18 | 1.55 (1.32-1.86) | 1.76 (1.51-2.06) |
| $C_{1h}$, μg/mL | 10.92[b] | 12.81 | 12.10 | 1.17 (1.03-1.33) | 1.11 (0.98-1.26) |
| $C_{24h}$, μg/mL | 1.38 | 2.50 | 2.81 | 1.81 (1.47-2.22) | 2.04 (1.65-2.51) |
| CL, mL/min | 9.77 | 6.33 | 5.55 | 0.65 (0.55-0.76) | 0.57 (0.49-0.66) |
| Parameter | HM (SD)[c] | HM (SD)[c] | HM (SD)[c] | | |
| β-phase $t_{½}$, h | 9.67 (2.39) | 11.71 (3.42) | 15.07 (3.72) | — | — |

HI, hepatic insufficiency; GMR, geometric mean ratio; CI, confidence interval; $AUC_{0-\infty}$, area under the concentration–time profile over the interval of last quantifiable point to infinity; $C_{1h}$, concentration at 1 hour from the start of drug infusion; $C_{24h}$, concentration at 24 hours from the start of drug infusion; CL, clearance; HM, harmonic mean; $t_{½}$, half-life.

a. Geometric means are reported for $AUC_{0-\infty}$, $C_{1h}$, $C_{24h}$, and clearance.

b. Based on a sample size of 23 healthy subjects.

c. Harmonic means (jackknife standard deviation) are reported for β-phase $t_{½}$.

study participants reported a total of 49 nonserious, clinical adverse experiences after administration of the following doses of caspofungin: 24 reports after 50 mg, 10 reports after 35 mg, and 8 reports after 70 mg; and 7 adverse experiences were reported while off drug. Of the 49 nonserious adverse experiences, 24 were considered possibly drug related by the investigator after administration of the following doses of caspofungin: 11 reports after 50 mg, 8 reports after 35 mg, and 5 reports after 70 mg. The most common clinical adverse experiences were swelling at the IV site (5 reports) and irritation at the IV site (6 reports), which were considered either probably not or possibly drug related by the investigator. Burning and itching at the IV sites (1 report each) were also reported. Of the adverse experiences not related to local tolerability, somnolence was frequently reported and considered possibly drug related by the investigator. All of the clinical adverse experiences were mild in intensity and as such consistent with a grade I toxicity rating. No adverse experiences of moderate or severe intensity were reported during or following multiple dosing with IV caspofungin. One patient with mild HI was hospitalized for bronchitis 11 days after administration of the final dose of caspofungin, which was considered probably not drug related by the investigator. The following 2 healthy subjects had laboratory adverse experiences of increased liver transaminases, neither of which was considered drug related by the investigator: One subject had modestly elevated ALT values from days 4 to 21 during dosing with caspofungin, with values ranging between 55 and 70 U/L (normal range, 1-45 U/L; predose day 1 value, 38 U/L) and minimal day-to-day variation. The ALT levels had returned to within normal range by day 24, 10 days after the final dose of caspofungin. The elevated ALT was considered probably not drug related by the investigator. Although caspofungin is known to elevate liver enzymes, the rationale for the causality assessment was that the ALT increases stabilized while the subject received caspofungin. Another subject had elevated ALT values predose on day 1 (49 U/L) that increased modestly during dosing with caspofungin, with a peak value on day 8 of 69 U/L. This subject's ALT value on day 42 was 47 U/L, which was not a clinically significant elevation above the upper limit of normal (ULN). The elevated ALT was considered definitely not drug related by the investigator. The rationale for the causality assessment was that ALT was elevated at baseline, which argued against a drug-related relationship postdose. In both of these subjects, the elevations in ALT, which were at most 1.5 times the ULN, were consistent with a grade I toxicity rating as defined by a 1.25 to 2.5 times increase beyond ULN.

*Pharmacokinetic results.* The mean plasma concentration–time profiles obtained from patients with mild HI and comparisons with matched healthy control subjects on days 1, 7, and 14 are given in Figure 2. The results indicate that there was a modest, although not clinically significant, effect of mild HI on the pharmacokinetics of caspofungin following multiple doses. The mean pharmacokinetic parameters given in Table II show that the difference in $AUC_{0-24h}$ obtained in patients with mild HI and the matched controls was statistically significant on day 7 ($P = .008$) and day 14 ($P = .041$) and approached

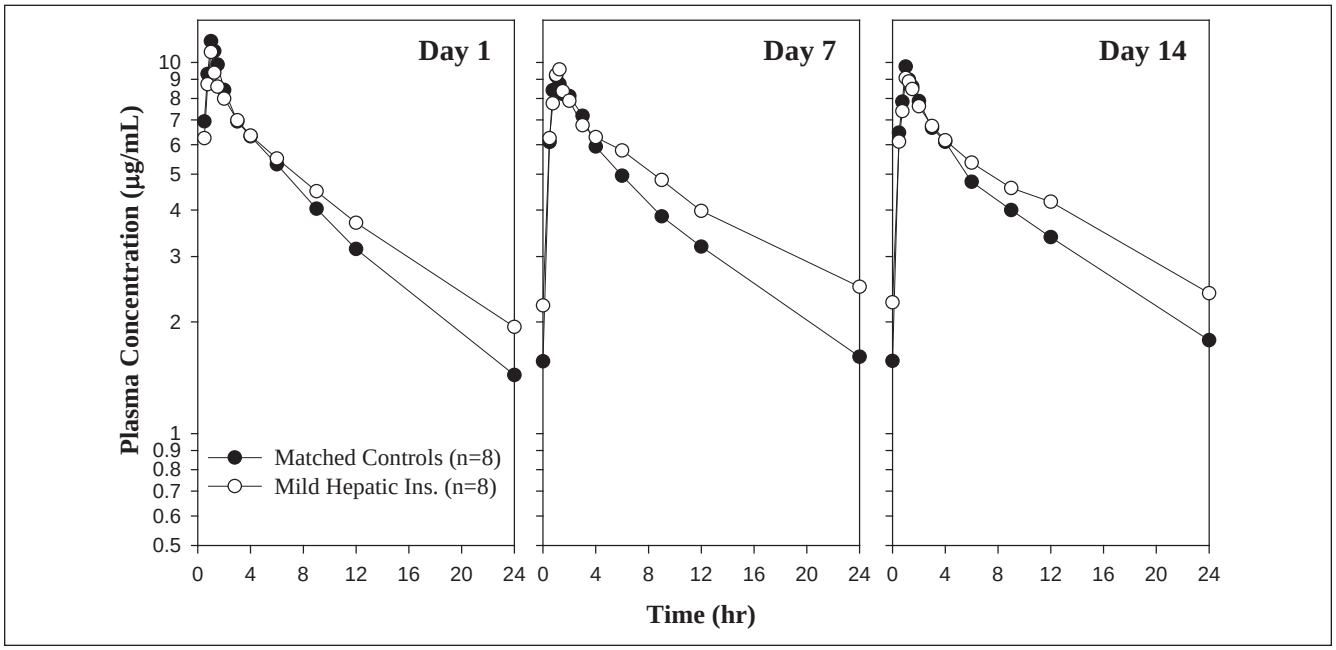


*Figure 2. Mean plasma concentration–time profiles in patients with mild hepatic insufficiency and matched healthy controls administered caspofungin 50 mg daily with a 70-mg loading dose.*

**Table II** Caspofungin Pharmacokinetics in Patients With Mild Hepatic Insufficiency and Matched Healthy Controls Administered 50 mg Daily With a 70-mg Loading Dose and in Patients With Moderate Hepatic Insufficiency Receiving a Reduced Dose of 35 mg Daily With a 70-mg Loading Dose and the Respective Healthy Control Subjects Receiving the Standard Regimen of 50 mg Daily With a 70-mg Loading Dose

| Pharmacokinetic Parameter | Least Squares Geometric Mean | | | | GMR (90% CI) Mild HI/Healthy Subjects | *P* Value[a] | Least Squares Geometric Mean | | | | GMR (90% CI) Moderate HI /Healthy Subjects | *P* Value[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mild HI | n | Healthy Subjects | | | n | Moderate HI | n | Healthy Subjects | | |
| Day 1 $AUC_{0\text{-}24h}$, µg·h/mL | 8 | 103.70 | 8 | 88.72 | 1.17 (1.03-1.33) | .053 | 8 | 132.94 | 8 | 106.21 | 1.25 (1.08-1.45) | .020 |
| Day 7 $AUC_{0\text{-}24h}$, µg·h/mL | 8 | 110.71 | 8 | 87.90 | 1.26 (1.11-1.43) | .008 | 8 | 116.89 | 8 | 102.69 | 1.14 (0.95-1.36) | .215 |
| Day 14 $AUC_{0\text{-}24h}$, µg·h/mL | 8 | 107.59 | 8 | 89.26 | 1.21 (1.04-1.39) | .041 | 8 | 116.22 | 8 | 108.27 | 1.07 (0.90-1.28) | .492 |
| Day 1 $C_{1h}$, µg/mL | 8 | 10.87 | 8 | 10.92 | 1.00 (0.89-1.11) | .953 | 8 | 12.58 | 8 | 13.03 | 0.97 (0.83-1.12) | .687 |
| Day 7 $C_{1h}$, µg/mL | 8 | 9.35 | 8 | 9.03 | 1.03 (0.93-1.15) | .588 | 8 | 8.57 | 8 | 10.75 | 0.80 (0.69-0.92) | .013 |
| Day 14 $C_{1h}$, µg/mL | 8 | 9.15 | 8 | 9.52 | 0.96 (0.83-1.11) | .633 | 8 | 8.82 | 8 | 11.43 | 0.77 (0.64-0.92) | .025 |
| Day 1 $C_{24h}$, µg/mL | 8 | 1.96 | 8 | 1.30 | 1.50 (1.20-1.88) | .007 | 8 | 3.19 | 8 | 1.58 | 2.01 (1.64-2.47) | <.001 |
| Day 7 $C_{24h}$, µg/mL | 8 | 2.53 | 8 | 1.49 | 1.70 (1.36-2.13) | .001 | 8 | 3.04 | 8 | 1.78 | 1.71 (1.32-2.21) | .003 |
| Day 14 $C_{24h}$, µg/mL | 8 | 2.40 | 8 | 1.67 | 1.44 (1.15-1.79) | .014 | 8 | 2.93 | 8 | 1.95 | 1.50 (1.16-1.93) | .015 |

HI, hepatic insufficiency; GMR, geometric mean ratio; CI, confidence interval; $AUC_{0\text{-}24h}$, concentration–time profile calculated over the interval 0 to 24 hours; $C_{1h}$, concentration at 1 hour from the start of drug infusion; $C_{24h}$, concentration at 24 hours from the start of drug infusion.

a. *P* value calculated for testing the difference between patients with hepatic insufficiency and healthy subjects.

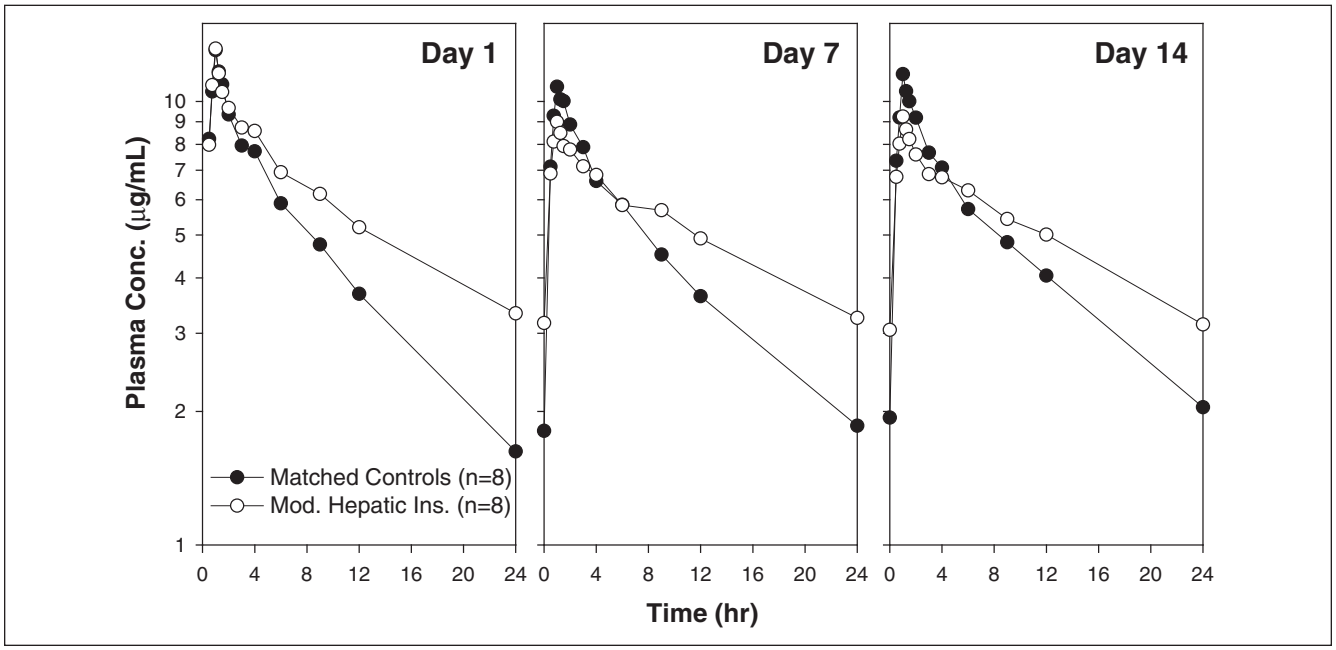


*Figure 3. Mean caspofungin plasma concentration–time profiles in patients with moderate hepatic insufficiency receiving a reduced dose of 35 mg daily with a 70-mg loading dose relative to control subjects receiving the standard maintenance dose of 50 mg daily with a 70-mg loading dose.*

significance on day 1 ($P = .053$). For $C_{24h}$, statistically significant differences were obtained on day 1 ($P = .007$), day 7 ($P = .001$), and day 14 ($P = .014$). On average, $AUC_{0\text{-}24h}$ was increased 17%, 26%, and 21%, and $C_{24h}$ was increased 50%, 70%, and 44%, in patients with mild HI relative to controls on days 1, 7, and 14, respectively (Table II). No statistically significant differences in $C_{1h}$ were seen on any of the days. β-phase half-life was increased 7% (11.12 hours vs 10.43 hours) relative to the matched controls. The 90% CI of the day 14 AUC GMR was contained within the (0.7-1.5) interval defining a lack of clinically significant alteration.

The mean plasma concentration–time profiles on days 1, 7, and 14 obtained from patients with moderate HI receiving a reduced maintenance dose were compared with profiles from matched healthy control subjects receiving the standard maintenance dose in Figure 3. The mean pharmacokinetic parameters given in Table II show that on day 14, as well as on days 1 and 7, the 90% CI for the geometric mean $AUC_{0\text{-}24h}$ ratio was contained within the interval (0.7-1.5), prespecified in the hypothesis as defining a lack of clinically meaningful alteration. Therefore, the reduced maintenance dose of 35 mg was proposed in patients with moderate HI.

On day 1, when HI patients and the control subjects both received a 70-mg loading dose, there was a moderate effect of moderate HI on the pharmacokinetics of caspofungin as indicated by statistically significant elevations in $AUC_{0\text{-}24h}$ ($P = .020$) and $C_{24h}$ ($P < .001$) of 25% and 101%, respectively. There was no statistically significant difference in $C_{1h}$ on day 1. On days 7 and 14, when the hepatic patients had received a reduced maintenance dose relative to controls, average concentrations were similar in both groups. That is, there were no statistically significant differences in $AUC_{0\text{-}24h}$ in HI patients receiving the dose reduction and controls receiving the standard regimen, and the point estimates of the GMR (HI/healthy) were close to 1. There were statistically significant reductions in $C_{1h}$ ($P = .013$ and $P = .025$, respectively) and statistically significant increases in $C_{24h}$ ($P = .003$ and $P = .015$, respectively) on days 7 and 14. On average, $C_{1h}$ was reduced 20% and 23%, and $C_{24h}$ was increased 71% and 50%, in patients with moderate HI relative to controls on days 7 and 14. Following the last dose of caspofungin in the multiple-dose study, the β-phase half-life increased 57% (16.28 hours vs 10.39 hours) in patients with moderate HI relative to the matched controls.

## DISCUSSION

Caspofungin pharmacokinetics are primarily controlled by uptake transport into hepatocytes and possibly other tissue cells.[10,11] The effect of HI on this uptake process was unknown; therefore, the pilot single-dose study was conducted to investigate the drug's safety and tolerability and to make an initial assessment of the impact of HI on caspofungin disposition. The definitive multiple-dose study was conducted to further investigate safety and tolerability and to assess whether mild HI caused a clinically significant alteration in caspofungin pharmacokinetics and to test a proposed reduced maintenance dose (from 50 to 35 mg) in moderate HI. A lack of clinically significant alteration in caspofungin pharmacokinetics was predefined as the 90% CI of the AUC GMR being contained within the interval (0.7-1.5). 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 mg or 70 mg of caspofungin, although this difference was not statistically significant.[4,5] The caspofungin dose of 35 mg produced concentrations that were ~70% of the value obtained with 50 mg in the efficacy study, thus supporting the lower bound of 0.7. Although no dose-limiting toxicities have been observed for caspofungin,[8] the upper bound of 1.5 comes from the ~50% increase in AUC seen in patients treated with 70 mg versus 50 mg. The 70-mg dose has been well tolerated in a large number of patients.[4,5,8]

Single and multiple IV doses of caspofungin were generally well tolerated in patients with mild and moderate HI as well as healthy subjects. As expected, both studies had reports of infusion site reactions, not uncommon for a drug with an IV route of administration. None of the reported serious or nonserious adverse experiences required dose interruption or adjustment in healthy subjects or patients with mild or moderate HI. The only 2 laboratory adverse experiences were increased ALT in 2 healthy subjects that remained ≤2-fold the ULN during the full course of dosing with caspofungin and returned to predose values following the completion of dosing. No patients with either mild or moderate HI experienced clinically significant increases in liver transaminases following daily dosing for 2 weeks with caspofungin.

In the pilot single-dose study, mild HI and moderate HI were found to moderately increase the exposure of caspofungin following 70-mg doses. The $AUC_{0-\infty}$ was increased by 55% and $C_{24h}$ by 81% in patients with mild HI, and $AUC_{0-\infty}$ was increased by 76% and $C_{24h}$ by 104% in patients with moderate HI relative to a historical control group. Thus, the multiple-dose HI study was undertaken to further investigate the effect of HI using a more definitive study design, including multiple-dose administration of caspofungin and the enrollment of matched control subjects within the same study so that a dosing recommendation could be made.

In the multiple-dose study, mild HI had a modest effect on the pharmacokinetics of caspofungin, which included a slight lengthening of the β-phase half-life and modest elevations in $AUC_{0-24h}$ and $C_{24h}$ relative to matched control subjects. This effect did not appear to be clinically meaningful because the upper limit of the 90% CI for the increase of $AUC_{0-24h}$ on days 1, 7, and 14 of multiple dosing was less than 1.5-fold. The increase in $C_{24h}$, without an increase of comparable magnitude of AUC or $C_{1h}$, was not considered to pose a safety issue. The effect of mild HI on caspofungin pharmacokinetics was of lesser magnitude than that observed in the single-dose study. Mild HI increased $C_{24h}$ 81% following the 70-mg dose in the single-dose study and only 50% following the 70-mg dose on day 1 of the multiple-dose study. Additionally, the magnitude of the effect of mild HI on β-phase half-life was greater in the single-dose study (21% increase) than in the multiple-dose study (7% increase). These differences between the 2 studies in the magnitude of the effect of mild HI are not large and were consistent with the range of results that would generally be expected for 2 studies with small numbers of patients (n = 6-8). Based on the results from the multiple- dose HI study, no dose adjustment is recommended for mild HI. Although the single-dose study indicated a somewhat greater effect of mild HI, it is believed that the results from the multiple-dose study are the appropriate results from which to determine whether a dose adjustment is needed for the following reasons: First, the second (multiple-dose) study was a more definitive evaluation of the effect of HI because it was a multiple-dose study that evaluated the effect of HI under approximate steady-state conditions and because it determined the effect relative to matched-control subjects enrolled in the same study rather than historical control subjects. Second, recommending no dose reduction, as indicated by the results of the multiple-dose study, was a more conservative approach for patients being treated for a life-threatening disease, such as invasive aspergillosis.

In the multiple-dose study, based on the pharmacokinetic results from the pilot single-dose study, a dose reduction was proposed for the patients with moderate HI. The proposed dose reduction for patients with moderate HI was 35 mg daily following the 70-mg loading dose on day 1. The primary pharmacokinetic parameter, AUC, obtained on days 7 and 14 in moderate HI patients, receiving the dose reduction, and controls, receiving the standard regimen of 50 mg daily after the 70-mg loading dose, was similar, and the geometric mean AUC ratios and 90% CI were contained within the interval (0.7-1.5) on all days. The dose reduction was designed to match average concentrations over the dosing interval (ie, AUC). Therefore, the reduced $C_{1h}$ and increased $C_{24h}$ in patients with moderate HI receiving the dose reduction are as expected; they result from the reduced dose and the smaller peak-to-trough ratio generated by the longer half-life in the moderate HI patients. In moderate (and mild) HI, the increase in $C_{24h}$, without an increase of comparable magnitude of AUC or $C_{1h}$, was not considered to pose a safety issue.

The effect of moderate HI on caspofungin pharmacokinetics was consistent between the single-dose study and multiple-dose study. The magnitude of the effect of moderate HI on $C_{24h}$ following the 70-mg dose in the single-dose study and the 70-mg dose on day 1 of the current multiple-dose study was similar (104% and 101% increase, respectively, relative to controls). There was a comparably minimal effect of moderate HI on $C_{1h}$ following the 70-mg dose in both studies (3% decreased in both studies). Finally, the magnitude of the effect of moderate HI on β-phase half-life was similar in both studies (56% and 57% increase, respectively, relative to controls). It is interesting to note that the 76% increase in $AUC_{0-\infty}$ obtained in the single-dose study would imply that a 43% reduction (reciprocal of 1.76 is 0.57) in dose would be necessary to adjust for the effect of moderate HI. The 30% dose reduction (from 50 mg to 35 mg) used in the multiple-dose study, resulting in very similar $AUC_{0-24h}$ in both patients with moderate HI and controls, suggests that the $AUC_{0-\infty}$ following single doses may somewhat overestimate the magnitude of pharmacokinetic effects on caspofungin at steady state.

Because the uptake transporter OATP1B1 (OATP-C) is thought to play a significant role in controlling caspofungin disposition,[10,11] the decreased clearance and increased caspofungin concentrations in patients with mild and moderate HI suggest that uptake transporter function in hepatocytes is somewhat diminished in patients with HI. The subsequent disposition step for caspofungin after cellular uptake involves a slow chemical (nonenzymatic) degradation to the ring-opened form.[10] It is possible that the single-dose pharmacokinetics somewhat overpredict the impact of HI on multiple dosing because the slow degradation acts as an alternate pathway over long-term dosing, given that it is not necessary for the drug to be taken up into hepatocytes for this first biotransformation step to occur.

In summary, caspofungin was generally well tolerated when single and multiple doses were administered to patients with mild and moderate HI. Because mild HI only modestly increased plasma concentrations (21% to 26% for AUC) following 50 mg of caspofungin once daily with a 70-mg loading dose on day 1, no dose adjustment is recommended. For moderate HI, a dose reduction to 35 mg of caspofungin once daily following the 70-mg loading dose on day 1 is recommended because it resulted in an AUC over the dosing interval similar to that obtained in subjects with normal hepatic function receiving the standard regimen of 50 mg once daily with a 70-mg loading dose on day 1.

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