Brief Report

Pharmacokinetic Characteristics of Caspofungin in Two Pediatric Liver Transplant Patients

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ABSTRACT

Background: The pharmacokinetic characteristics of the antifungal drug caspofungin have not been reported in children.

Objective: The aim of this study was to report limited caspofungin pharmacokinetic data for pediatric liver transplant patients.

Methods: Two pediatric liver transplant patients, aged 5 years (not dialyzed) and 9 months (dialyzed), were assessed. Using a novel, validated, liquid-phase extraction with high-performance liquid chromatography, we measured plasma caspofungin concentrations from blood samples obtained within a 24-hour period after the patients were given 1 mg/kg IV of caspofungin.

Results: Noncompartmental analysis for the nondialyzed patient showed an elimination half-life of 10.7 hours, a volume of distribution of 0.11 L/kg, and a systemic clearance of 0.12 mL/min/kg. Liver enzyme activities increased briefly; the increase may have been due to concomitant graft rejection. For the dialyzed patient, the half-life was 11.7 hours, with an adjusted volume of distribution of 0.18 L/kg and a systemic clearance of 0.24 mL/min/kg. No clinically relevant treatment-related adverse events were noted.

Conclusions: Pharmacokinetic data found in the 2 patients in this study are similar to those reported in adults. Until more thorough data are published, caspofungin 1 mg/kg may be considered a reasonable, tolerable dose for children. (*Curr Ther Res Clin Exp.* 2003;64:127–136) Copyright © 2003 Excerpta Medica, Inc.

Key words: caspofungin, pharmacokinetics, child, liver transplant.

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INTRODUCTION

Caspofungin acetate is a member of the echinocandin class of novel antifungal drugs approved for the treatment of aspergillosis in adult patients refractory to or intolerant of conventional therapy and for human immunodeficiency virus-associated candidal esophagitis. Unique among antifungal therapeutic classes, echinocandins target a fungal macromolecule within the cell wall, circumventing pathogen cross-resistance.¹ Echinocandin-mediated inhibition of the synthesis of (1,3)-beta-glucan, a glucose polymer essential for the structural integrity of many fungal pathogens, damages the cell wall and ultimately causes cellular lysis.²⁻⁴ The activity spectrum of these drugs is still being defined, but in vitro activity includes *Candida* spp.; *Aspergillus* spp.; *Histoplasma capsulatum*; *Blastomyces dermatitidis*; *Pneumocystis carinii*; some lesser known filamentous and dimorphic fungi; and, possibly, *Coccidioides immitis* and *Sporothrix schenckii*. Fungi that have only small amounts of (1,3)-beta-glucan, such as *Cryptococcus neoformans* and the Mucorales order, are resistant to the echinocandins.

Human pharmacokinetic data on caspofungin obtained from healthy male adult volunteers have been published⁵ and are also available on the package insert.⁶ After a brief early distributional phase, the drug is cleared from plasma in a linear fashion (first order), with a half-life ($t_{1/2}$) of 9 to 10 hours, which primarily reflects ongoing distribution from plasma to extravascular sites. A longer terminal elimination $t_{1/2}$ of 40 to 50 hours is observed. With repeated higher doses, mild accumulation of drug occurs such that steady state is not achieved until after 3 weeks of dosing. This dose-dependent time to reach steady state suggests saturable distribution or elimination mechanisms. Caspofungin is 97% bound to albumin. The drug is highly metabolized in the liver, although it does not appear to be mediated by the cytochrome (CYP) 450 system. Elimination of a single radiolabeled dose yields 35% fecal and 41% urinary radioactivity, but only 1.4% of the drug in the urine is the parent compound. The recommended adult dose for patients without liver failure is a loading dose of 70 mg IV on the first day, followed by single daily doses of 50 mg IV. In adults, this dosing regimen results in a total drug exposure, as measured by area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}), of 100.5 mg-h/L. No adjustment is required for renal failure, but the loading dose should be reduced to 50 mg for patients with moderate hepatic insufficiency. Dosing guidelines for patients with severe hepatic insufficiency are not yet available.

According to a MEDLINE search for articles containing the terms *caspofungin* and *pharmacokinetics* published up until November 2002, no data have yet been published on the pharmacokinetic characteristics of caspofungin in children. We report herein a limited pharmacokinetic analysis of the drug in 2 critically ill pediatric liver transplant patients, performed within the context of a clinical pharmacology consultative service.

PATIENTS AND METHODS

Patient 1

At the time of consultation, patient 1 was a 5-year-old Caucasian boy with a history of biliary atresia, who failed Kasai biliary shunt and had undergone orthotopic liver transplant 1 month earlier. The patient's posttransplant course was complicated by biliary anastomosis breakdown, which required intraoperative repair and broad-spectrum antibiotics. Two days later he developed an intestinal perforation and peritonitis that required additional surgery and placement of abdominal drains. Cultures of the drainage were positive for both *Candida glabrata* and *Enterococcus faecium*. *C glabrata* was susceptible to amphotericin B (minimum inhibitory concentration [MIC] <1 µg/mL) but resistant to fluconazole (MIC >64 µg/mL). Amphotericin B desoxycholate 1 mg/kg IV daily was added to his antibiotic regimen.

During the subsequent 2 weeks, this patient's clinical course was marked by ongoing signs of peritonitis complicated by frequent episodes of hemorrhage from the gastrointestinal (GI) tract. A massive hemorrhage rendered him hypotensive, with subsequent renal failure necessitating continuous venovenous hemodialysis. Amphotericin B was changed to the liposomal form because of the renal failure.

Although the patient's renal function returned to normal shortly thereafter, he developed a low-grade fever and an increased peripheral leukocyte count, both of which worsened despite treatment with vancomycin hydrochloride and meropenem. Therefore, despite negative intraoperative and abdominal drainage cultures, ongoing occult fungal infection was a concern, and increased antifungal activity was desired. Due to prior isolation of fluconazole-resistant *C glabrata* and the GI toxicity of flucytosine, caspofungin was selected.

Patient 2

Patient 2 was a 9-month-old African American infant, born at 31 weeks' gestation, who had received an orthotopic liver transplant for the treatment of biliary atresia 2 weeks prior to the time of consultation. His initial transplant did not function well, and due to ongoing hepatorenal failure, he received a second transplant 4 days after the first. The early postoperative period was complicated by GI bleeding and hypotension. During the next several days, he became anuric and developed seizures. Findings on electroencephalography and magnetic resonance imaging were consistent with severe brain injury. He was maintained on a ventilator and continuous venovenous hemodialysis. Two weeks after his second transplant, liver enzyme activities increased suddenly and dramatically, and he underwent open liver biopsy and exploration. Intraoperative cultures of the liver surface were also positive for *C glabrata*. Postoperative acidosis and temperature instability developed. Because of his renal failure, caspofungin was initially started at a daily dose of 1 mg/kg, infused over 1 hour, but on the basis of subsequent pharmacokinetic analysis, was increased to 2.0 mg/kg daily.

Methods

Cognizant of the lack of pediatric pharmacokinetic, efficacy, and tolerability data, we explained the risks (including failure of therapy and hepatic injury) and potential benefits to the families of both patients. After obtaining permission from the parents to start therapy with caspofungin, for both patients we decided to perform a limited pharmacokinetic analysis to ensure that total drug exposure (as measured by AUC_{0-24}) was similar to that achieved in adults.^{5,6} Because these patients were not participating in a study, and because they were critically ill, the number of blood samples was limited.

All blood samples were obtained with arterial catheters not used for drug infusion. Caspofungin 1 mg/kg was infused through a central IV catheter over 1 hour. For patient 1, blood samples of 1 mL each were obtained before starting the drug and, beginning at the time of his fifth dose, immediately before the infusion (representing a trough); immediately after the infusion (representing a peak); and 6, 12, and 22 hours after the end of the infusion (representing a second trough). For patient 2, samples were collected prior to receiving the drug, immediately before his third dose, at the end of the infusion, and 6 and 12 hours after the end of the infusion. A fifth sample (the trough) was not drawn due to miscommunication. Samples were collected in tubes containing lithium heparin and stored at 4°C for a maximum of 6 hours before analysis.

Pharmacokinetic Analysis

Our analytic method was loosely based on that of Schwartz et al⁷ and has been submitted for publication. It uses liquid-phase extraction from heparinized plasma and high-performance liquid chromatography with fluorescent detection. The assay was developed as part of ongoing experiments to determine the pharmacokinetic/pharmacodynamic relationships of echinocandins.

Standard curves were established by plotting the ratio of drug/internal standard peak height versus known plasma drug concentration on a logarithmic scale and line fitting by least-squared residual error. Intraday and interday precision and accuracy of the method were determined by triplicate analyses of plasma standards. After validation of the assay, 0.1-mL samples of the patients' plasma were prepared and analyzed. Because the patients were receiving other drugs at the time of analysis, "blank" plasma samples, obtained just before starting caspofungin treatment, were analyzed to verify that no competing peaks had occurred.

Due to the limited number of samples, only noncompartmental pharmacokinetic parameter estimations were made, including elimination rate constant, volume of distribution (V_d), total plasma clearance (CL), and AUC from 0 to 24 hours (AUC_{0-24}). All calculations were performed using the Kinetica™ 2000 software package (InnaPhase Corp., Paris, France).

The Pediatric Intensive Care Unit flow sheets for each patient were monitored daily by the primary physician and one of the authors (M.N.) for the occurrence of adverse events while receiving caspofungin, and for 3 days afterward. These

flow sheets contained hourly information on temperature, heart rate, blood pressure, respiratory rate, fluid balance, laboratory results (eg, chemistry panels), and therapeutic interventions such as dialysis.

RESULTS

Chromatography

Caspofungin and internal standard were detectable by fluorescence at the lowest and highest ranges of plasma standards (ie, 0.2 and 30.0 $\mu\text{g/mL}$, respectively), without interference from exogenous or endogenous compounds. The patients' concurrent medications at the time of analysis are listed in Table I. Retention times for caspofungin and internal standard were 8.5 and 10.2 minutes, respectively. Assay precision varied between 1.9% and 7.2%, and accuracy varied between 89.0% and 106.7%.

Pharmacokinetic Characteristics

Both patients received caspofungin 1 mg/kg infused IV over 1 hour. Patient plasma caspofungin concentrations are shown in Figure 1. Pharmacokinetic parameters and comparison data for adults are reported in Table II. The maximum and minimum concentrations, $t_{1/2}$, AUC_{0-24} , CL, for patient 1 were similar to those reported for adult patients. In contrast, those for patient 2 were different. Maximum and minimum concentrations and AUC_{0-24} were 40.2%, 41.0%, and 50.3% of typical adult values, respectively, and V_d and CL were 218.1% and 155.0%, respectively. The volume of the dialysis circuit was ~85 mL, which significantly increased the circulating blood volume and, consequently, V_d . Based on patient 2's body weight, a corrected V_d would be 0.18 L/kg. Furthermore, V_d tends to be larger in infants than in older children, which may have been contributory.

Tolerability Assessment

On a dosing regimen of 1 mg/kg IV daily, patient 1 experienced a mild, clinically insignificant increase in serum bilirubin concentration and serum aminotransfer-

Table I. Concurrent patient treatments at the time of caspofungin assay. (These treatments did not interfere with the assay.)

Acyclovir	Morphine sulfate
Bumetanide	Mycophenolate mofetil
Co-trimoxazole	Phytonadione
Fentanyl citrate	Ranitidine
Heparin sulfate	Tacrolimus
Intralipids	Total parenteral nutrition
Liposomal amphotericin B	Ursodiol
Meropenem	Vancomycin hydrochloride
Methylprednisolone	Zolpidem tartrate

Figure 1. Plasma caspofungin concentration versus time after 1 mg/kg IV infused over 1 hour. The dotted line for patient 2 represents a projection based on pharmacokinetic parameters calculated from measured plasma caspofungin concentrations.

ase activities (Figure 2). Serum albumin concentration was low (2.4–3.1 mg/dL) but stable before, during, and after caspofungin therapy. International Normalized Ratio (INR) was elevated (1.67–2.24) but also did not change in response to caspofungin therapy. Hepatic synthetic function, as measured by serum albumin concentration and INR, remained stable. Because of the increase in serum bilirubin concentration and serum aminotransferase activities causing

Table II. Comparison between the patients' caspofungin pharmacokinetic parameters and corresponding reported adult values.

Pharmacokinetic Parameter	Patient 1*	Patient 2†	Adult Values ^{§‡}
C_{max} , mg/L	8.80	4.00	9.94
C_{min} , mg/L	1.2–2.0	0.8	1.4–2.7
$t_{1/2}$, h	10.7	11.7	9–10
AUC_{0-24} , mg-h/L	135.6	50.6	100.5
CL, mL/min/kg	0.12	0.24	0.14–0.17 [§]
V_d , L/kg	0.11	0.24	0.11

C_{max} = maximum concentration; C_{min} = minimum concentration; $t_{1/2}$ = half-life; AUC_{0-24} = area under the plasma concentration–time curve from 0 to 24 hours; CL = clearance; and V_d = volume of distribution.

*Caspofungin 1 mg/kg was infused over 1 hour; the blood sample analyzed was drawn on day 5.

†Caspofungin 1 mg/kg was infused over 1 hour; the blood sample analyzed was drawn on day 4.

‡Caspofungin was administered at an initial loading dose of 70 mg, followed by 50 mg daily; the blood sample analyzed was drawn on day 14.

§Assuming an average body weight of 70 kg.

||Calculated using $CL = \text{dose}/AUC_{0-24}$ and $V_d = t_{1/2} \times CL/0.693$, assuming an average body weight of 70 kg.

Figure 2. Markers of hepatic inflammation in patient 1. AST = aspartate aminotransferase; ALT = alanine aminotransferase.

concerns about drug-related hepatotoxicity, and because of the lack of documented ongoing fungal infection, treatment was stopped. However, the patient also was experiencing persistent GI bleeding that, after cessation of caspofungin, was subsequently found to arise from the aortohepatic shunt, raising the question of whether his increases in markers of hepatic inflammation were secondary to hypoperfusion of the organ. Furthermore, his fever and increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels also were consistent with mild transplant rejection, and he received several large steroid pulses just before and after the last dose of caspofungin. Therefore, transplant rejection also may have played a role in the abnormal laboratory findings. Apart from these issues, the drug was well tolerated, with no local or systemic reactions reported.

In patient 2, albumin (range, 2.2–3.6 mg/dL), INR (range, 1.04–1.50), AST (range, 125–236 U/L), ALT (range, 62–163 U/L), and total bilirubin (range, 1.6–3.3 mg/dL) fluctuated without trend throughout the 2-week course of caspofungin treatment.

DISCUSSION

According to our MEDLINE search, this is the first report of caspofungin pharmacokinetic analysis in children. Moreover, the children in this analysis were critically ill liver transplant patients with preexisting hepatic dysfunction, as evidenced by elevated serum bilirubin concentration and INR and persistent hypoalbuminemia.

The results of this limited caspofungin pharmacokinetic analysis in these 2 children were consistent with pharmacokinetic data in adults.⁵ A physiologic

hypothesis for the increased caspofungin clearance in patient 2 relates to differences between adults and children. Given the large, polar nature; high protein binding; and high hepatic clearance of caspofungin, dialysis is unlikely to be effective in removing the drug. Although infants <3 months of age generally have slower plasma drug clearance rates due to immaturity in glomerular filtration, renal tubular secretion, and hepatic drug-metabolizing capacity, drug clearance rates often are higher in young children than in older children and adults.^{8,9} Caspofungin may have cleared in this infant more rapidly than in the older child or adults for this reason, but it is important not to generalize too much from 1 or 2 patients, especially when their clinical status (ie, acutely ill in intensive care) is different from that of the comparators (ie, healthy adult volunteers).^{5,6}

Clearly, the number of samples from these patients was insufficient to adequately describe the complete pharmacokinetic profile of caspofungin, nor was that our reason for performing the analysis. Our data suggest that, even after 5 days of dosing, drug accumulation continues to occur; the same effect also was noted in adult patients.⁵ In patient 1, the first trough was 1.2 mg/L and the second trough was 2.0 mg/L. If truly at steady state, these values should have been equivalent. Even with correction for assay variability, the second trough was 30% higher. Therefore, our estimates of clearance may be too high compared with estimates at steady state.

The issue of tolerability was muddled in patient 1. Caspofungin is extensively metabolized by the liver and, therefore, might be expected to exhibit hepatotoxicity. Animal studies with other echinocandins do show hepatotoxic effects, but only at extremely high doses that are >10-fold the standard dose. In clinical trials in adults, caspofungin caused a mild, reversible increase in serum aminotransferase activities 2-fold of normal in up to 10% of patients.⁶ Patient 1, but not patient 2, also showed mild increases in AST and ALT, as well as serum bilirubin concentration, but no increase in INR or decrease in serum albumin concentration. Concurrently, patient 1 may have been experiencing rejection or inadequate perfusion of the transplanted liver. Certainly, he was not exposed to larger, more toxic amounts of drug by overdosing or poor elimination. With clinical use thus far, caspofungin has not demonstrated significant toxicity.

Although caspofungin does not appear to interact with the CYP450 system, certain reported drug-drug interactions suggest that it might affect the time-course of some drugs mediated by CYP3A4. Merck & Co., Inc. (West Point, Pennsylvania) has reported in early clinical trials that individuals taking tacrolimus and caspofungin concurrently had a 26% decrease in the 12-hour tacrolimus trough concentration.⁶ Both of our patients received tacrolimus and caspofungin concomitantly. The tacrolimus plasma concentrations in patient 1 increased from 5.3 to 9.3 ng/mL after 3 doses of caspofungin, and then decreased to 5.7 ng/mL after the last 2 doses. After completing caspofungin treatment, his plasma tacrolimus concentrations were ~7 ng/mL. Overall, therefore, the 2 patients

were unaffected by caspofungin. Patient 2 received tacrolimus erratically during the time of concurrent caspofungin treatment, making it difficult to discern any drug-drug interaction.

Three weeks after his last dose of caspofungin, patient 1 died of a massive GI hemorrhage. *Candida* were not isolated from autopsy specimens. Patient 2 developed *C glabrata* fungemia, and his blood could not be sterilized despite an increase in his caspofungin dose to 2 mg/kg. The MIC, as measured by National Committee for Clinical Laboratory Standards M27-A protocol¹⁰ for antifungal susceptibility testing of yeasts, was 2.0 mg/L. When liposomal amphotericin B was added to his regimen, his blood was sterilized within 48 hours.

CONCLUSIONS

We have documented that caspofungin at a daily dose of 1 mg/kg IV given to a 5-year-old patient with mild hepatic failure resulted in plasma concentrations within the range of those expected on the basis of adults administered a 70-mg loading dose followed by 50 mg daily. The same dose of caspofungin given to a 9-month-old infant on hemodialysis resulted in low plasma caspofungin concentrations due to the increased volume in the dialysis circuit. Therefore, caspofungin 1 mg/kg may be considered a reasonable starting point for dosing, at least in children with some degree of hepatic dysfunction, until more definitive recommendations are published.

The drug appeared to be well tolerated, but we cannot exclude the possibility in patient 1 that mild, clinically insignificant increases in serum aminotransferase activity and serum bilirubin concentration were drug related. Therefore, we recommend that these parameters be monitored, particularly in children with any degree of liver failure. Clearly, these data are extremely limited, and more pharmacokinetic data in children are required. A clinical trial is ongoing to provide this information.

Finally, on the basis of patient 2's inability to clear his candidemia with caspofungin alone, a caspofungin MIC of 2.0 mg/L may be near a future susceptibility breakpoint. This is, of course, highly speculative and also deserves further investigation.

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