COMPARISON OF CASPOFUNGIN AND AMPHOTERICIN B FOR INVASIVE CANDIDIASIS

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ABSTRACT

Background Caspofungin is an echinocandin agent with fungicidal activity against candida species. We performed a double-blind trial to compare caspofungin with amphotericin B deoxycholate for the primary treatment of invasive candidiasis.

Methods We enrolled patients who had clinical evidence of infection and a positive culture for candida species from blood or another site. Patients were stratified according to the severity of disease, as indicated by the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and the presence or absence of neutropenia and were randomly assigned to receive either caspofungin or amphotericin B. The study was designed to compare the efficacy of caspofungin with that of amphotericin B in patients with invasive candidiasis and in a subgroup with candidemia.

Results Of the 239 patients enrolled, 224 were included in the modified intention-to-treat analysis. Base-line characteristics, including the percentage of patients with neutropenia and the mean APACHE II score, were similar in the two treatment groups. A modified intention-to-treat analysis showed that the efficacy of caspofungin was similar to that of amphotericin B, with successful outcomes in 73.4 percent of the patients treated with caspofungin and in 61.7 percent of those treated with amphotericin B (difference after adjustment for APACHE II score and neutropenic status, 12.7 percentage points; 95.6 percent confidence interval, −0.7 to 26.0). An analysis of patients who met prespecified criteria for evaluation showed that caspofungin was superior, with a favorable response in 80.7 percent of patients, as compared with 64.9 percent of those who received amphotericin B (difference, 15.4 percentage points; 95.6 percent confidence interval, 1.1 to 29.7). Caspofungin was as effective as amphotericin B in patients who had candidemia, with a favorable response in 71.7 percent and 62.8 percent of patients, respectively (difference, 10.0 percentage points; 95.0 percent confidence interval, −4.5 to 24.5). There were significantly fewer drug-related adverse events in the caspofungin group than in the amphotericin B group.

Conclusions Caspofungin is at least as effective as amphotericin B for the treatment of invasive candidiasis and, more specifically, candidemia. (N Engl J Med 2002;347:2020-9.)

THE optimal first-line treatment for serious candida infections is a controversial issue. Amphotericin B has served as standard treatment for five decades,[1-3] but toxic effects often limit its use.[2] Fluconazole has a role in the treatment of candidemia.[4-10] Prospective, randomized studies have shown that fluconazole is as effective as amphotericin B, with superior safety, for the treatment of candidemia in patients without neutropenia.[11-13] However, certain non-albicans candida species, which account for over half the cases of candidemia, are less susceptible to fluconazole.[14-18]

The need remains for new agents to treat serious candida infections. One alternative is caspofungin, an echinocandin with fungicidal activity against candida.[19,20] Caspofungin targets the fungal cell wall, and it retains activity against isolates with resistance to azoles or polyenes.[21-26] The absence of this target in mammalian cells probably contributes to its favorable safety profile.[26-29] We compared caspofungin with amphotericin B for the treatment of invasive candidiasis. The trial was conducted between November 1997 and June 2001 at 56 institutions in 20 countries.

METHODS

Selection of Patients

Patients were eligible for enrollment in the study if they were over the age of 18 years and had had one or more positive candida cultures from blood or another, sterile site within the previous four days. Patients with positive cultures of urine specimens, sputum specimens, bronchoalveolar-lavage specimens, oropharyngeal or esophageal specimens, or samples from indwelling drains were excluded. An additional criterion for enrollment was at least one of the following clinical signs of infection during the previous two days: fever (a temperature that exceeded 101°F [38.3°C] or two readings that exceeded 100°F [37.8°C]), clinically significant hypothermia (a temperature of less than 96.8°F [36.0°C]), hypotension (systolic blood pressure, <90 mm Hg or a decrease ≥30 mm Hg), or signs of inflammation at a candida-infected site. Patients with suspected endocarditis, osteomyelitis, or meningitis were excluded. Patients who had received antifungal therapy for more than two days (cu-

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mulative dose of amphotericin B, >2 mg per kilogram of body weight; lipid amphotericin B, >10 mg per kilogram; or fluconazole, >1600 mg) were also excluded. Patients receiving rifampin, ritonavir, or cyclosporine were also not enrolled.

The study protocol was approved by the institutional review board of each participating institution, and written informed consent was obtained from all patients before enrollment.

Study Design

Patients were stratified according to the presence or absence of neutropenia and the score on the Acute Physiology and Chronic Health Evaluation (APACHE II) (≤20 or >20). They were randomly assigned to receive either intravenous caspofungin or intravenous amphotericin B according to a schedule maintained by each participating institution's pharmacist. The schedules were generated by computer to ensure equivalent randomization at each site. Patients and investigators were unaware of the treatment assignments. Patients who were assigned to receive caspofungin were given a 70-mg loading dose, followed by 50 mg per day. Patients who were assigned to receive amphotericin B and who did not have neutropenia were given 0.6 to 0.7 mg per kilogram per day; those with neutropenia received 0.7 to 1.0 mg per kilogram per day. A double-dummy technique was used to maintain the blinding. The daily treatment regimen consisted of infusion of caspofungin or matching placebo (saline) for one hour, immediately followed by infusion of amphotericin B or matching placebo (saline with a multivitamin complex) for two or more hours. An increase (or reduction) in the dose was not permitted.

Patients were to receive antifungal therapy for 14 days after the most recent positive candida culture. A minimum of 10 days of intravenous therapy was required. After 10 days, intravenous therapy was continued or oral fluconazole was substituted (400 mg per day). Fluconazole was given only to patients who did not have neutropenia, whose clinical condition had improved, whose follow-up cultures had been negative for 48 hours, and whose candida isolates were susceptible to fluconazole. Patients with *Candida krusei* or *C. glabrata* infection continued to receive intravenous therapy.

Symptoms or signs of candida infection (including the most abnormal temperature) were documented daily during the treatment regimen and two weeks and six to eight weeks after treatment. Physical examination and laboratory tests were performed twice a week during treatment and at both follow-up visits. For patients with candidemia, two samples for blood cultures were obtained daily until the results had been negative for at least 48 hours. For nonblood infections, follow-up cultures were also routinely obtained; however, in certain patients, the infection was assumed to have been eradicated and follow-up cultures were not required if there was no longer any clinical or radiographic evidence of infection. Retinal examinations for candida endophthalmitis were performed by ophthalmologists before enrollment, at the end of intravenous therapy, and at the final follow-up visit.

Evaluation of Efficacy

Efficacy was assessed in terms of the overall response to treatment. A favorable overall response was defined as the resolution of all symptoms and signs of candida infection and culture-confirmed eradication (or presumptive eradication for certain nonblood infections). The outcome was considered to be unfavorable if the infection was clinically or microbiologically unresponsive, if the study drug was withdrawn before there was documented improvement, or if toxic effects necessitated a change in antifungal therapy. Evaluations were performed on day 10 of intravenous therapy, at the end of intravenous therapy, at the end of all antifungal therapy (intravenous therapy and oral fluconazole), and at both follow-up visits. The primary time point for the determination of efficacy was the end of intravenous therapy. During the six-to-eight-week period after treatment, a patient was considered to have a relapse if an invasive candida infection had recurred or if antifungal therapy for a proven or suspected candida infection was again administered.

Statistical Analysis

The study was primarily designed to determine whether caspofungin was as effective as amphotericin B for the treatment of invasive candidiasis, with efficacy measured in terms of the overall response at the end of intravenous therapy. The observed outcome was adjusted for the two stratification variables (the presence or absence of neutropenia and the APACHE II score) according to the Cochran–Mantel–Haenszel method. The noninferiority of caspofungin would be demonstrated if the two-sided 95.6 percent confidence interval for the difference in efficacy between the two treatment groups (the response to treatment in the caspofungin group minus the response in the amphotericin B group), adjusted for neutropenic status and the APACHE II score, included 0 and the lower boundary was not lower than −20.0 percent. The superiority of caspofungin would be demonstrated if the confidence interval was entirely above 0. Assuming a response rate of 70 percent in the amphotericin B group ($\alpha=0.05$, $\beta=0.1$, and $\delta=0.20$), we calculated that 110 patients per treatment group were needed to test for noninferiority. A noninferiority analysis was also performed for patients with candidemia; approximately 85 such patients per treatment group were required ($\beta=0.2$). Adjustments for multiple comparisons were not performed.

The two prespecified study populations for the analysis of efficacy were the patients included in the modified intention-to-treat analysis and the population of patients who met prespecified criteria for evaluation. The modified intention-to-treat analysis (the primary analysis) included patients who had a documented diagnosis of invasive candidiasis and who received the study treatment for at least one day. The prespecified criteria for evaluation were inclusion in the modified intention-to-treat analysis and no concomitant antifungal therapy, no protocol violations that might interfere with the assessment of efficacy, an appropriate evaluation at the end of treatment, and receipt of the study treatment for at least five days.

The study was also designed to compare certain end points in an analysis of safety, including nephrotoxicity. A nephrotoxic effect was defined as at least a doubling of the serum creatinine level, or an increase of at least 1.0 mg per deciliter (88.4 mmol per liter) if the base-line level was elevated. Other predefined end points in the analysis of safety included drug-related adverse events, discontinuation of treatment due to drug-related adverse events, infusion-related toxic effects, and hypokalemia requiring potassium supplementation. All patients who received the assigned study treatment were included in the safety analysis. An independent data safety monitoring board monitored both safety and efficacy during the study. The authors who are not affiliated with Merck had access to all the study data, take responsibility for the accuracy of the analysis, and had authority over the preparation of the manuscript and the decisions about publication.

RESULTS

Base-Line Characteristics of the Patients

A total of 239 patients were enrolled in the study over a period of 44 months, 224 of whom were included in the modified intention-to-treat analysis (Table 1). The base-line characteristics of the patients were similar in the two treatment groups (Table 2). Because of the stratification method, the groups did not differ significantly with respect to neutropenic status ($P=0.32$) or the mean APACHE II score ($P=0.46$). The majority of the patients had candidemia, but peritonitis and intraabdominal abscesses were not uncom-

TABLE 1. NUMBERS OF PATIENTS ENROLLED, INCLUDED IN THE MODIFIED INTENTION-TO-TREAT ANALYSIS, AND INCLUDED IN THE ANALYSIS OF PATIENTS WHO MET PRESPECIFIED CRITERIA FOR EVALUATION.

GROUP	CASPOFUNGIN	AMPHOTERICIN B
	no. of patients	
Total	114	125
Candida culture not positive	2	2
No evidence of invasive infection	2	4
Sterility of the sample not confirmed	0	4*
<1 Full day of treatment with study drug	1	0
Included in modified intention-to-treat analysis	109	115
<5 Days of intravenous therapy	9	5
Concomitant antifungal therapy†	1	1
Indeterminate evaluation at the end of therapy‡	2	2
Other protocol violations		
Positive culture for more than 7 days before enrollment	2	1
Central venous catheter not removed	2	1
Prior antifungal therapy that exceeded the maximum allowed§	1	2
Wrong treatment dose	4	6
Included in analysis of patients who met prespecified criteria for evaluation	88	97

*The four patients had positive candida cultures, but they were obtained from a preexisting, indwelling peritoneal drain in three of the patients and from pleural fluid in the presence of a communicating esophageal–pleural leak in the fourth.

†Both patients received oral fluconazole (50 to 100 mg per day) for oropharyngeal candidiasis.

‡The two patients receiving caspofungin were excluded because the assessment was complicated by aspergillus pneumonia (in one patient) and inoperable bile obstruction (in the other). The two patients receiving amphotericin B were excluded because the assessment of symptoms was complicated by klebsiella pneumonia.

§The total allowable dose was 1600 mg of fluconazole, 2 mg of amphotericin B per kilogram of body weight, or 10 mg of lipid amphotericin B per kilogram.

mon. Approximately 60 percent of the patients had received prior antifungal therapy, but only for a day or less in most cases.

Candida Isolates

The most common candida isolate was *C. albicans* (Table 3), which accounted for 35.6 percent of infections in the caspofungin group and 54.1 percent of those in the amphotericin B group (P=0.009). *C. parapsilosis* was isolated in 19.8 percent of the patients in the caspofungin group and 18.3 percent of those in the amphotericin B group, *C. tropicalis* in 19.8 percent and 12.8 percent, *C. glabrata* in 12.8 percent and 9.2 percent, and *C. krusei* in 4.0 percent and 0.9 percent, respectively. Five patients had infections with both *C. albicans* and other candida species.

Duration of Treatment

The duration of treatment was similar in the two groups (P=0.60). Patients in the caspofungin group were treated for a mean of 12.1 days (median, 11.0; range, 1 to 28), and those in the amphotericin B group were treated for a mean of 11.7 days (median, 10.0; range, 1 to 28). A switch to oral fluconazole (after day 10) occurred in the cases of 27 caspofungin-treated patients (24.8 percent) and 40 amphotericin B–treated patients (34.8 percent).

Efficacy

In the modified intention-to-treat analysis, the proportion of patients with a favorable response at the end of intravenous therapy was 73.4 percent in the caspofungin group and 61.7 percent in the amphotericin B group (Table 4); after adjustment for neutropenic status and the APACHE II score, the difference in the proportion of patients with a favorable response was 12.7 percentage points (95.6 percent confidence interval, −0.7 to 26.0; P=0.09). In the analysis of patients who met the prespecified criteria for evaluation, 80.7 percent of the caspofungin-treated patients and 64.9 percent of the amphotericin B–treated patients had successful outcomes at the end of intravenous therapy. The difference between the treatment groups for this analysis was 15.4 percentage points (95.6 percent confidence interval, 1.1 to 29.7; P=0.03). The outcomes were consistent among the stratified subgroups. In both treatment groups, the response rate was lower among patients with indicators of a poor prognosis (neutropenia or an APACHE II score higher than 20) than among patients without these

TABLE 2. BASE-LINE CHARACTERISTICS OF THE 224 PATIENTS INCLUDED IN THE MODIFIED INTENTION-TO-TREAT ANALYSIS.*

CHARACTERISTIC	CASPOFUNGIN (N=109)	AMPHOTERICIN B (N=115)
Sex — no. (%)		
Male	56 (51.4)	69 (60.0)
Female	53 (48.6)	46 (40.0)
Age — yr		
Median	56	55
Range	17–84	18–81
APACHE II score		
≤20 — no. (%)	88 (80.7)	92 (80.0)
>20 — no. (%)	21 (19.3)	23 (20.0)
Mean score	14.8	15.4
Neutropenia — no. (%)†		
Yes	14 (12.8)	10 (8.7)
No	95 (87.2)	105 (91.3)
Underlying disease — no. (%)‡		
Diabetes mellitus	25 (22.9)	21 (18.3)
Active leukemia or lymphoma	16 (14.7)	13 (11.3)
Renal failure or insufficiency	23 (21.1)	30 (26.1)
HIV infection (any stage)	4 (3.7)	3 (2.6)
Risk factors for invasive candidiasis — no. (%)§		
Recent use of broad-spectrum antibiotics	90 (82.6)	102 (88.7)
Recent use of a central venous catheter	80 (73.4)	90 (78.3)
Recent surgery	54 (49.5)	58 (50.4)
Recent hyperalimentation	39 (35.8)	55 (47.8)
Underlying malignant condition	30 (27.5)	38 (33.0)
Immunosuppressive therapy	28 (25.7)	18 (15.7)
Receipt of a transplant	6 (5.5)	1 (0.9)
Site of infection — no. (%)		
Blood (candidemia)	90 (82.6)	91 (79.1)
Peritoneal fluid	8 (7.3)	8 (7.0)
Abscess	4 (3.7)	9 (7.8)
Pleural fluid	1 (0.9)	2 (1.7)
Lung (biopsy-proven)	1 (0.9)	0
Skin (biopsy-proven)	0	1 (0.9)
Multiple sites¶	5 (4.6)	4 (3.5)
Prior antifungal therapy — no. (%)		
No	48 (44.0)	38 (33.0)
Yes‖	61 (56.0)	77 (67.0)
<1 day	44	54
1–2 days	14	21
>2 days	3	2

*None of the differences between the treatment groups were statistically significant.

†Neutropenia was defined as an absolute neutrophil count of less than 500 per cubic millimeter.

‡Some patients had more than one underlying condition. HIV denotes human immunodeficiency virus.

§For use of broad-spectrum antibiotics, use of a central venous catheter, and hyperalimentation, recent was defined as within 14 days before screening; for surgery, recent was defined as within 30 days before screening. Some patients had more than one risk factor.

¶Five patients had candidemia and infection at another site, and four patients had infection at two nonblood sites.

‖The total dose for less than 1 day was 800 mg or less of fluconazole or another azole, 60 mg or less of amphotericin B, or 300 mg or less of a lipid amphotericin B formulation; for one to two days, 801 to 1600 mg of fluconazole or another azole, 61 to 120 mg of amphotericin B, or 301 to 600 mg of lipid amphotericin B; and for more than two days, more than 1600 mg of fluconazole or another azole, more than 120 mg of amphotericin B, or more than 600 mg of lipid amphotericin B. Prior therapy in the caspofungin group included amphotericin B (in 32 patients), an azole (in 22), lipid amphotericin B (in 1), and a combination of an azole and amphotericin B (in 6). Prior therapy in the amphotericin B group included amphotericin B (in 45 patients), an azole (in 27), and a combination of an azole and amphotericin B (in 5).

TABLE 3. BASE-LINE CANDIDA ISOLATES.*

ISOLATE	CASPOFUNGIN	AMPHOTERICIN B
	percentage of patients	
Candida albicans	35.6	54.1
C. parapsilosis	19.8	18.3
C. tropicalis	19.8	12.8
C. glabrata	12.8	9.2
C. krusei	4.0	0.9
C. guilliermondii	3.0	0.9
C. lipolytica	1.0	0
C. rugosa	1.0	0
Multiple species†	3.0	3.7

*Differences between the treatment groups were not statistically different except for the proportion of patients with *C. albicans* isolates (P=0.009).

†Two patients in the caspofungin group had *C. albicans* and *C. glabrata*, and one patient had *C. parapsilosis* and *C. guilliermondii*. In the amphotericin B group, one patient each had *C. albicans* and *C. glabrata*, *C. albicans* and *C. lusitaniae*, *C. albicans* and *C. tropicalis*, and *C. krusei*, *C. glabrata*, and *C. tropicalis*.

indicators, but there was still a trend in favor of caspofungin.

The outcomes stratified according to the candida pathogen were generally similar in the two groups. For *C. albicans*, the rate of a favorable response was 63.9 percent in the caspofungin group and 57.6 percent in the amphotericin B group. The response rate was higher among patients with non-albicans infections in both the caspofungin group (80.0 percent) and the amphotericin B group (68.0 percent). The responses were similar for the most common non-albicans species — namely, *C. parapsilosis* (70.0 percent and 65.0 percent), *C. tropicalis* (85.0 percent and 71.4 percent), and *C. glabrata* (76.9 percent and 80.0 percent).

At each of the four other time points (day 10, the end of antifungal therapy, two weeks after treatment, and six to eight weeks after treatment), the percentage of patients with successful outcomes was higher in the caspofungin group than in the amphotericin B group (Table 4).

Persistent or Recurrent Infection

Similar proportions of patients in the two treatment groups had persistently positive cultures, persistent signs or symptoms, or new metastatic lesions or withdrew from the study after four or fewer days (Table 5). A larger proportion of patients in the amphotericin B group had toxic effects requiring a change in therapy (P=0.03).

The proportion of patients with a relapse was similar in the two treatment groups (Table 5). Only five patients had a relapse of candidemia (three in the caspofungin group and two in the amphotericin B group). In all five patients, the organism cultured at relapse and the base-line isolate were identical with respect to the species and the minimal inhibitory concentration.

Site of Infection

The study was specifically designed to compare the efficacy of caspofungin and that of amphotericin B for the treatment of candidemia. In the modified intention-to-treat analysis, the proportion of patients with candidemia who had a favorable outcome at the end of intravenous therapy was 71.7 percent in the caspofungin group and 62.8 percent in the amphotericin B group. The difference, adjusted for neutropenic status and the APACHE II score, was 10.0 percentage points (95.0 percent confidence interval, −4.5 to 24.5; P=0.22). In the analysis of patients with candidemia at base line who met the prespecified criteria for evaluation, 80.3 percent of the caspofungin-treated patients and 64.6 percent of the amphotericin B–treated patients had a successful outcome at the end of intravenous therapy. In this analysis, the difference was 15.2 percentage points (95.0 percent confidence interval, −0.6 to 31.0; P=0.06).

A larger proportion of patients in the caspofungin group than in the amphotericin B group had multiple positive blood cultures at base line (58.7 percent vs. 48.9 percent). However, the percentages of patients with blood cultures that were still positive on days 4 and 7 of intravenous therapy did not differ significantly between the two groups (day 4: 19.6 percent in the caspofungin group and 19.1 percent in the amphotericin B group; day 7: 12.0 percent and 8.5 percent, respectively).

The outcomes were also examined in patients without candidemia. Among those with peritonitis, the response rate was 100 percent (eight of eight patients) in the caspofungin group and 87.5 percent (seven of eight) in the amphotericin B group; among those with intraabdominal abscesses, the response rate was 75.0 percent (three of four) and 33.3 percent (three of nine), respectively. Of the nine patients with multiple sites of infection, four of the five patients treated with caspofungin (80.0 percent) and all four treated with amphotericin B (100 percent) had a favorable response.

Central Venous Catheters

Management of central venous catheters did not differ significantly between the two groups. Overall, 111 patients with candidemia (54 in the caspofungin group and 57 in the amphotericin B group) had an indwelling central venous catheter at the time of the first positive blood culture. By day 3, the central venous catheter had been removed in 41 of the caspo-

TABLE 4. FAVORABLE RESPONSES TO TREATMENT.

TIME POINT	MODIFIED INTENTION-TO-TREAT ANALYSIS		PATIENTS WHO MET CRITERIA FOR EVALUATION	
	CASPOFUNGIN (N=109)	AMPHOTERICIN B (N=115)	CASPOFUNGIN (N=88)	AMPHOTERICIN B (N=97)
	no. with a favorable response/total no. (%)			
End of intravenous therapy	80/109 (73.4)	71/115 (61.7)	71/88 (80.7)	63/97 (64.9)*
Absolute neutrophil count at enrollment				
<500/mm³	7/14 (50.0)	4/10 (40.0)	6/8 (75.0)	3/8 (37.5)
≥500/mm³	73/95 (76.8)	67/105 (63.8)	65/80 (81.2)	60/89 (67.4)
APACHE II score				
≤20	68/88 (77.3)	61/92 (66.3)	61/76 (80.3)	53/78 (67.9)
>20	12/21 (57.1)	10/23 (43.5)	10/12 (83.3)	10/19 (52.6)
Day 10 of intravenous therapy†	66/75 (88.0)	64/75 (85.3)	59/67 (88.1)	55/64 (85.9)
At end of all antifungal therapy	79/109 (72.5)	71/115 (61.7)	70/88 (79.5)	63/97 (64.9)‡
2 Weeks after treatment§	56/88 (63.6)	56/104 (53.8)	52/72 (72.2)	49/86 (57.0)
6–8 Weeks after treatment§	47/83 (56.6)	47/99 (47.5)	44/67 (65.7)	41/82 (50.0)

*P=0.03 for the difference between the two treatment groups.

†Only patients who received 10 days of intravenous therapy were included in the analysis.

‡P=0.05 for the difference between the two treatment groups.

§Treatment failures at the end of intravenous therapy were counted as treatment failures at all subsequent time points. Unfavorable responses after the end of intravenous therapy included all treatment failures at the primary time point and any relapses up until that point. Patients who had favorable responses at the end of intravenous therapy but subsequently withdrew from the study or were lost to follow-up were excluded from subsequent analyses unless a relapse was documented before withdrawal or loss to follow-up.

fungin-treated patients (75.9 percent) and 42 of the amphotericin B–treated patients (73.7 percent); guidewire changes were made in 7 patients (13.0 percent) and 10 patients (17.5 percent), respectively. The response rate among the 11 patients whose central venous catheters were not removed or changed (6 in the caspofungin group and 5 in the amphotericin B group) was similar to the rate among the patients whose central venous catheters were removed or changed.

Mortality

The mortality rate among all patients was similar in the two treatment groups. There were 39 deaths in the caspofungin group (34.2 percent) and 38 in the amphotericin B group (30.4 percent, P=0.53). The proportion of patients who died during intravenous therapy was also similar in the two groups. The death of one patient (a patient in the amphotericin B group who had a cardiac arrest) was judged to be drug-related.

A post hoc analysis was performed to determine mortality attributable to candida. Patients were considered to have died from candida infection if any of the following criteria were met: the investigator identified the candida infection as the cause of death, the patient had a positive candida culture within 48 hours of death, or there was histopathological evidence of candida or a positive culture at autopsy. Overall, five of the caspofungin-treated patients (4.4 percent) and nine of the amphotericin B–treated patients (7.2 percent) died from candida infection (P=0.57).

Candida Endophthalmitis

An eye examination was performed in 217 of the patients (96.9 percent); 187 patients (83.5 percent) underwent a base-line examination, and 155 (69.2 percent) underwent one or more follow-up examinations. Only seven patients (3.7 percent) had candida endophthalmitis at base line; resolution was noted in all patients with follow-up examination. One patient in the amphotericin B group who had normal findings at base line reported ocular disturbances on day 3; a follow-up eye examination confirmed the presence of endophthalmitis.

Susceptibility of Candida Isolates

The base-line candida isolates from 94 percent of the patients were evaluated for in vitro susceptibility to antifungal agents at a central microbiology laboratory according to the methods of the National Committee for Clinical Laboratory Standards (document 27A). The minimal inhibitory concentration of caspofungin for the various candida species ranged from 0.125 to more than 8 μg per milliliter, as follows: *C. albicans* (median, 0.5 μg per milliliter; range, 0.125 to >8), *C. glabrata* (1.0 μg per milliliter; range, 0.5 to 2), *C. tropicalis* (1.0 μg per milliliter; range, 0.5

TABLE 5. TREATMENT FAILURES AND RELAPSES (MODIFIED INTENTION-TO-TREAT ANALYSIS).

FAILURE OR RELAPSE	CASPOFUNGIN (N=109)	AMPHOTERICIN B (N=115)
	no. (%)	
Failure at end of therapy	29 (26.6)	44 (38.3)
Persistently positive cultures	9 (8.3)	10 (8.7)*
Candida albicans	3	8
C. glabrata	1	0
C. krusei	0	1
C. parapsilosis	5†	0
C. albicans and *C. lusitaniae*	0	1
New metastatic candida lesions	4 (3.7)	5 (4.3)
Brain	1	0
Eye	0	1
Liver, spleen, or both	2	2
Lung (biopsy proven)	0	1
Joint	0	1
Skin	1	0
Persistent signs or symptoms despite negative cultures	6 (5.5)	5 (4.3)
Toxic effect requiring change in antifungal therapy	3 (2.8)	19 (16.5)‡
Withdrawal from study after ≤4 days (no definite improvement, failure, or other indeterminate)	7 (6.4)	5 (4.3)
Relapse 6 to 8 weeks after treatment	7 (6.4)	8 (7.0)
Recurrent candidemia	3 (2.8)	2 (1.7)
C. albicans	2	1
C. glabrata	0	1
C. tropicalis	1	0
Recurrent nonblood infection	2 (1.8)	0
C. albicans	1	
C. glabrata	1	
Symptoms treated with systemic antifungal therapy	1 (0.9)	6 (5.2)
New abscess (culture not positive, no treatment administered)	1 (0.9)	0

*Three patients in this group also had toxic effects that contributed to their withdrawal from the study.

†Four of the five patients were enrolled at the same site within a four-month period. All the isolates had similar minimal-inhibitory-concentration patterns for caspofungin, amphotericin B, and fluconazole.

‡P=0.03 for the difference between the two treatment groups.

to >8), *C. parapsilosis* (2 μg per milliliter; range, 2 to >8), and *C. krusei* (2 μg per milliliter; all values were 2). All the isolates for which the minimal inhibitory concentration of caspofungin exceeded 8 μg per milliliter were associated with trailing end points; this trailing effect was not noted when a different medium, antibiotic medium no. 3, was used for susceptibility testing. The minimal inhibitory concentration of amphotericin B ranged from 0.25 to 2.0 μg per milliliter. The outcome of treatment was not predicted by the base-line minimal inhibitory concentration; all isolates for which the minimal inhibitory concentration of caspofungin exceeded 2 μg per milliliter responded favorably to caspofungin.

Adverse Events

The proportion of patients with drug-related adverse events was significantly higher in the amphotericin B group than in the caspofungin group (Table 6). Fever, chills, and infusion-related events were much more frequent in the amphotericin B group. One patient in the caspofungin group (0.9 percent), as compared with 40 patients in the amphotericin B group (32.0 percent), had infusion-related adverse events of moderate or severe intensity. Significantly more patients in the amphotericin B group had nephrotoxic effects (24.8 percent, vs. 8.4 percent in the caspofungin group) or hypokalemia (23.4 percent vs. 9.9 percent).

DISCUSSION

Our trial was designed to compare the efficacy of an echinocandin with that of amphotericin B in patients with invasive candidiasis at various sites, as well as in those with candidemia. Inclusion in the study required evidence of proven invasive candidiasis, according to established guidelines.[30] The study design and outcome evaluations mirrored those used in prior stud-

TABLE 6. DRUG-RELATED ADVERSE EVENTS AND OTHER SAFETY END POINTS.

VARIABLE	CASPOFUNGIN (N=114)	AMPHOTERICIN B (N=125)	P VALUE
	no./total no. (%)		
Clinical events	33/114 (28.9)	73/125 (58.4)	0.002
Chills	6/114 (5.3)	33/125 (26.4)	0.003
Fever	8/114 (7.0)	29/125 (23.2)	0.01
Hypertension	2/114 (1.8)	8/125 (6.4)	
Phlebitis or thrombophlebitis	4/114 (3.5)	6/125 (4.8)	
Tachycardia	2/114 (1.8)	13/125 (10.4)	
Nausea	2/114 (1.8)	7/125 (5.6)	
Vomiting	4/114 (3.5)	10/125 (8.0)	
Tachypnea	0/114	13/125 (10.4)	
Rash	1/114 (0.9)	4/125 (3.2)	
Laboratory abnormalities*	27/111 (24.3)	67/124 (54.0)	0.002
Elevated serum alanine aminotransferase	4/109 (3.7)	10/123 (8.1)	
Elevated serum aspartate aminotransferase	2/108 (1.9)	11/122 (9.0)	
Elevated serum alkaline phosphatase	9/109 (8.3)	19/122 (15.6)	
Elevated total serum bilirubin	3/109 (2.8)	11/124 (8.9)	
Elevated blood urea nitrogen	2/108 (1.9)	19/120 (15.8)	0.02
Elevated serum creatinine	4/109 (3.7)	28/124 (22.6)	0.05
Decreased serum potassium	11/111 (9.9)	29/124 (23.4)	0.04
Decreased hemoglobin	1/111 (0.9)	13/124 (10.5)	
Clinical event or laboratory abnormality	48/114 (42.1)	94/125 (75.2)	0.002
Withdrawal because of adverse event	3/114 (2.6)	29/125 (23.2)	0.003
Infusion-related event	23/114 (20.2)	61/125 (48.8)	0.002
Hypokalemia requiring supplementation within 72 hr after onset	13/114 (11.4)	33/125 (26.4)	0.02
Nephrotoxic effect†	8/95 (8.4)	26/105 (24.8)	0.02

*The denominator for each laboratory abnormality is dependent on the number of patients who had at least one evaluation for that laboratory test following the start of intravenous therapy.

†A nephrotoxic effect was defined as a serum creatinine level that was twice the base-line value or higher, or an increase of at least 1 mg per deciliter (88.4 μmol per liter) in patients with a base-line serum creatinine level above the upper limit of the normal range. Patients with a creatinine clearance of less than 30 ml per minute were excluded from this analysis.

ies, except that our study was double-blinded and included patients with neutropenia.[4,5,11-13]

Except for a difference in the proportion of patients with *C. albicans* infections, the two treatment groups were well matched. In the modified intention-to-treat analysis, caspofungin was as effective as amphotericin B at the end of intravenous therapy. In the analysis of patients who met the prespecified criteria for evaluation, caspofungin was superior to amphotericin B. Differences in efficacy between the two groups were mainly a reflection of failures due to toxic effects (in 3 percent of the caspofungin group and 17 percent of the amphotericin B group). There were no significant differences in relapse or mortality rates in the two groups at the final follow-up visit.

Over 80 percent of the patients in our study had candidemia, and the outcomes in this subgroup mirrored the overall results, as did the outcomes in patients with infections at sites other than the blood. The rate of a favorable response to caspofungin among patients with postsurgical infections, including candida peritonitis and intraabdominal abscesses, was high.

A significantly larger percentage of patients treated with amphotericin B had infusion-related adverse events, nephrotoxic effects, or hypokalemia. The incidence of adverse events in the two groups was similar to that in two previous, dose-ranging studies that compared caspofungin with amphotericin B.[27,28]

Although patients with neutropenia were not excluded from the study, only 11 percent of the enrolled patients had neutropenia at base line. Thus, the outcome data for these patients must be interpreted with caution. The poor prognosis for patients with neutropenia, the fact that the study was blinded, and unfamiliarity with echinocandins among clinicians may have accounted for the low proportion of patients with neutropenia among those enrolled. As expected, the response rate was lower among patients with neutropenia than among those without neutropenia in both treatment groups. The most common cause of treatment failure in the cohort of patients with neutropenia was the development of metastatic (in most cases hepatosplenic) candida lesions after granulocytic recovery.

In our study, the incidence of non-albicans infections (55 percent) was considerably higher than that in the initial comparative studies of amphotericin B and fluconazole (25 to 35 percent).[11,12] Recent epidemiologic changes in the microbiologic characteristics of candida infections may account in large part for this difference.[15-18] The international composition of the study may also have contributed to the difference. For instance, the enrollment of patients in Latin American countries accounted for most *C. parapsilosis* infections.[15,31,32] Finally, there may have been a bias against the inclusion of patients with *C. albicans* infections, with clinicians opting to use fluconazole to treat immunocompetent patients infected with this organism.

Among patients with non-albicans candida infections, the outcomes were similar in the two groups. However, five of the nine caspofungin-treated patients with persistently positive cultures had *C. parapsilosis* candidemia. This finding was not associated with neutropenia, a high APACHE II score, or a delayed change of a central venous catheter. Four of these five patients were enrolled at the same institution within a four-month period. The minimal inhibitory concentrations of caspofungin (2 μg per milliliter), amphotericin B, and fluconazole were the same for the *C. parapsilosis* isolates from all four of these patients, suggesting that they were infected with the same strain or with closely related strains. In contrast, 12 of the 14 patients with *C. parapsilosis* infections at other institutions had favorable responses to caspofungin.

In this study, caspofungin was effective for the treatment of invasive candidiasis and, more specifically, candidemia. At each evaluation, the percentage of patients with a favorable outcome was higher in the caspofungin group than in the amphotericin B group. The outcomes at the end of intravenous therapy in the patients who could be evaluated suggest that caspofungin was superior to amphotericin B. Caspofungin is an effective, yet less toxic, alternative to amphotericin B for the treatment of invasive candidiasis.

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APPENDIX

In addition to the authors, the following investigators participated in the study: **Argentina** — P. Cahn (Fundacion Huesped, Buenos Aires), R.O. Ruvinski (Hospital Durand, Buenos Aires), A. Torres (Hospital Zenem Santillan, Tucuman); **Australia** — G. Dobb (Royal Perth Hospital, Perth), C. Eisen and J. Lipman (Royal Brisbane Hospital, Herston); **Austria** — W. Graninger (General Hospital of the City of Vienna, Vienna), W. Linkesh (University Clinic for Internal Medicine, Graz), N. Vetter (Pulmonologisches Zentrum der Stadt Wein, Vienna); **Belgium** — F. Jacobs (Hôpital Université Erasme, Brussels), B. Vandercam (Cliniques Universitaires Saint-Luc-Médecine, Brussels); **Canada** — G. Harding (St. Boniface General Hospital, Winnipeg, Man.), M. Laverdiere (Hospital Maisonneuve-Rosemont, Montreal), P. Phillips (St. Paul's Hospital, Vancouver, B.C.); **Colombia** — A. Villaneuva (Instituto de Seguros Sociales, Barranquilla); **France** — M. Leporrier (Centre Hospitalier Universitaire Clemenceau, Caen), Y. Ozier (Cochin Hospital, Paris), J.F. Rossi (Hôpital LaPeyronie, Montpellier); **Germany** — G. Just-Nuebling and W. Stille (University Hospital of Johann-Wolfgang-Goethe-University, Frankfurt); **Hong Kong** — R. Liang (Queen Mary Hospital, Hong Kong); **Israel** — M. Shapiro (Hadassah Medical Center, Jerusalem), A.M. Yinnon (Shaare-Zede Medical Center, Jerusalem); **Mexico** — J. Andrade-Perez (Santiago Nuevo Hospital Civil de Guadalajara, Guadalajara), J. Castenon-Gonzalez (Centro Medico Nacional Siglo XXII, Mexico Federal District); **the Netherlands** — I.M. Hoepelman (Academisch Ziekenhuis Utrecht, Utrecht), A. Voss (Academisch Ziekenhuis Nijmegen, Nijmegen); **Russia** — N. Klimko (Institute of Invasive Mycosis, St. Petersburg), V. Savchenko (Hematological Center of the Academy of Medical Sciences, Moscow); **Spain** — E. Bouza (Hospital Gregorio Maranon, Madrid), J.A. Carton (University of Oviedo, Oviedo), M. Gobernado-Serrano (Hospital La Fe, Valencia), A. Guerrero-Espejo, C.Q. Rodriquez-Navarro (Hospital Ramon y Cajal, Madrid), J.A. Martinez (Hospital Clinic I Provincial de Barcelona, Barcelona); **United Kingdom** — P. Hawkey (University of Leeds, Leeds); **United States** — R.D. Adam (University of Arizona Medical Center, Tucson), L. Cone (Eisenhower Medical Center, Rancho Mirage, Calif.), J.R. Graybill (Audie L. Murphy Memorial Veterans Hospital, San Antonio, Tex.), R. Greenberg (University of Kentucky Medical Center, Lexington), S. Gordon and K. Adal (Cleveland Clinic Foundation, Cleveland), E. Johnson (St. Michael's Medical Center, Newark, N.J.), S. Hadley (Beth Israel Deaconess Hospital, Boston), D. Hospenthal (Tripler Army Medical Center, Honolulu), D.G. Maki (University of Wisconsin Medical Center, Madison), J.E. Mangino (Ohio State University Hospital, Columbus), B. Myers (Mount Sinai Medical Center, New York), J. Pfundstein (Fairfax Hospital, Fairfax, Va.), I. Raad (M.D. Anderson Cancer Center, Houston), A.C. Reboli (Cooper Hospital–University Medical Center, Camden, N.J.), B. Segal (Buffalo General Hospital and Roswell Park Cancer Institute, Buffalo, N.Y.), J. Vazquez (Wayne State University, Detroit); **Venezuela** — J.R. Torres-Rojas (Clinica Santa Sofia, Caracas). **Data Safety and Monitoring Board** — H. Masur (chair, National Institutes of Health, Bethesda, Md.), M.P. Glauser (back-up chair, Centre Hospitalier Universitaire, Lausanne, Switzerland), S. Waldman (Thomas Jefferson University Hospital, Philadelphia), S. Petersdorf (University of Washington Medical Center, Seattle), C.E. Davis (University of North Carolina, Chapel Hill).

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