A Randomized, Double-Blind, Prospective Study of Caspofungin vs. Amphotericin B for the Treatment of Invasive Candidiasis in Newborn Infants

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Summary
Background: Caspofungin is an echinocandin agent with fungicidal activity against Candida species.
Objective: To assess the efficacy, safety and tolerability of caspofungin relative to amphotericin B in neonates with invasive candidiasis.
Patients and Methods: Thirty-two neonates with invasive candidiasis were randomly assigned to receive either caspofungin (n = 15) or amphotericin B (n = 17). Efficacy was evaluated, with a successful outcome defined as fulfilling all the components of a prespecified five-part composite endpoint. Evaluation of safety was done by monitoring drug-related adverse events.
Results: At the end of intravenous therapy, evaluation showed that caspofungin was superior, with a favorable response in 86.7% of patients as compared with 41.7% of those who received amphotericin B (p = 0.04). There were significantly fewer adverse events in the caspofungin group than in the amphotericin B group. Conclusion: Caspofungin is more effective, safer and alternative to amphotericin B for the treatment of invasive candidiasis in newborn infants.

Key words: caspofungin, amphotericin B, invasive candidiasis, neonates.

Introduction
Invasive candidiasis is an increasing problem in neonatal intensive care units (NICUs) worldwide and is an important cause of morbidity, mortality and prolonged hospital stay [1, 2]. These events have developed concurrently with a shift from Candida albicans to non-albicans species of Candida [3–6]. However, C. albicans remains the dominant species in most NICUs. Amphotericin B continues to be the mainstay of therapy for systemic fungal infections in NICU, but its use is limited by the risk of nephrotoxicity and hypokalemia. Fluconazole is active against most Candida species but is limited by emergence of resistance, particularly in non-albicans species of Candida [7].

Caspofungin is an echinocandin antifungal agent that non-competitively inhibits the synthesis of the β-(1,3)-D-glucan component of the cell wall of a number of clinically important fungi, including Aspergillus and Candida. It is active against many Candida isolates that are resistant to other antifungal agents, including fluconazole, fluclotaxine and amphotericin B [8]. Caspofungin is recommended for invasive candidiasis in adults, but has been poorly experienced in neonates and infants <12 months of age [9]. This study was designed to assess the efficacy, safety and tolerability of caspofungin relative to amphotericin B in neonates with invasive candidiasis.

Patients and Methods
We performed a prospective, randomized, double-blind study at the NICU of Aseer Central Hospital, Saudi Arabia, between October 2008 and September 2010. The study was approved by the ethics committee of the Hospital. Written informed consent was obtained from the parents before the study.

Acknowledgements
We thank the staff of the NICU of Aseer Central Hospital for their kind cooperation.
**Study design**

Neonates with confirmed invasive candidiasis who had at least one positive blood culture and/or positive cerebrospinal fluid culture or positive urine culture obtained by suprapubic aspiration were enrolled in the trial. Infants who had congenital malformations or elevated serum bilirubin, liver enzymes, alkaline phosphatase, serum creatinine were excluded.

Patients with invasive candidiasis were randomly assigned to receive either caspofungin or amphotericin B according to a schedule generated by computer to ensure equivalent randomization. The schedule was maintained by the participating pharmacist. The investigator and the treating nurses were unaware of the treatment assignments. Caspofungin (2 mg kg\(^{-1}\) day\(^{-1}\)) \(^{[1]}\) and amphotericin B (1 mg kg\(^{-1}\) day\(^{-1}\)) were administered by intravenous infusion for >1 h. Opaque covers were used to conceal the infusion bags and catheters used for infusions of the study therapy.

All patients were subjected to sepsis work-up, CT brain, renal ultrasound, bone scan, echocardiogram and ophthalmologic examination. Patients were to receive study therapy for at least 14 days. Duration of treatment of invasive candidiasis was determined according to The Infections Disease Society of America guidelines for the treatment of fungal infection in newborns \(^{[10]}\).

**Evaluation of efficacy**

Efficacy was assessed in the term of the overall response to treatment. The response was considered favorable if all five of the following criteria were met: successful treatment of invasive candidiasis based on the resolution of all symptoms and signs of fungal infection, culture-confirmed eradication, absence of any breakthrough fungal infection during therapy or within 7 days after completion of therapy, survival for 7 days after completion of therapy and no premature discontinuation of the study because of drug-related toxicity or lack of efficacy.

**Evaluation of safety**

The evaluation of safety and tolerability of caspofungin and amphotericin B was assessed by clinical review of all study events. We monitored patients for clinical adverse events daily during the administration of study therapy and for 14 days thereafter. Laboratory studies included serum bilirubin, liver enzymes, alkaline phosphatase, serum creatinine and serum electrolytes were performed at the time of enrollment of patients in the study as a base-line assay then twice weekly throughout the antifungal therapy and at both follow-up visits.

Evaluations were done at the five time endpoints, on Day 10 of intravenous therapy, at the end of intravenous study therapy, at the end of all antifungal therapy, at 2 weeks after treatment and at 6–8 weeks after treatment. We assessed whether any clinical or laboratory adverse events was related to the study therapy. The primary time point for determination of efficacy was the end of intravenous study therapy. A patient was considered to have a relapse if an invasive *Candida* infection had occurred or if antifungal therapy was again administered.

Endpoints in the analysis of safety included drug-related adverse events, discontinuation of the study drug due to drug-related adverse events, infusion-related toxic effects, hypokalemia requiring potassium supplementation and nephrotoxic effects. The outcome was considered unfavorable if the study drug was withdrawn due to drug-related adverse events. Infusion-related event was defined as the development of systemic symptoms during and 1 h after the infusion. A nephrotoxic effect was defined as a serum creatinine level that was twice the base-line value or higher.

**Statistical analysis**

Indices of safety and efficacy of caspofungin and amphotericin B were expressed as frequencies and proportions. Chi-square, Fisher’s exact and Student’s *t*-test were used as tests of significance at 5% level. Statistical analysis was performed by using (SPSS) software.

**Results**

A total of 32 neonates with invasive candidiasis were enrolled in the study (Fig. 1). Of the 32 patients, 7 (21.9%) infants had candida meningitis, 2 (6.2%) had ventriculitis, 9 (28.1%) had endocarditis, 5 (15.6%) had endophthalmitis, 7 (21.9%) had urinary candidiasis associated with or without fungal ball or renal abscess and 2 (6.2%) had osteomyelitis. Fifteen neonates received caspofungin and 17 infants received amphotericin B, and their clinical characteristics are shown in Table 1.

The most common *Candida* isolates was *C. albicans* which accounted for 73.3% of infections in the caspofungin group and 76.4% of those in the amphotericin B group (*p* > 0.05). *Candida parapsilosis* was isolated in 20% of patients in the caspofungin group and 11.8% of those in the amphotericin B group (*p* > 0.05; Table 2). *Candida albicans* was detected in all cases with fungal meningitis or ventriculitis. In patients with *Candida* endocarditis, *C. albicans* was isolated in six patients and *C. parapsilosis* was detected in three infants.

**Efficacy**

At the end of intravenous therapy, the efficacy of caspofungin was significantly higher than that of amphotericin B group, with successful outcomes in 86.7% of patients treated with caspofungin and in 41.7% of those treated with amphotericin B.
At each of the five time points of evaluation of efficacy, the percentage of patients with favorable responses was significantly higher in the caspofungin group than in the amphotericin B group. After the end of intravenous therapy, three patients in the caspofungin group withdrew from subsequent evaluation (one died, two were lost to follow-up). Five patients in the amphotericin B group withdrew from the subsequent analysis due to drug-related adverse events. At the final follow-up visit, none of the caspofungin-treated patients had relapse; however, 2 (11.8%) of the amphotericin B-treated neonates developed relapse ($p = 0.48$).

**Safety**

The overall drug-related clinical and laboratory adverse events were significantly lower in neonates who received caspofungin than in those who received amphotericin B ($p < 0.05$). None of these adverse events led to caspofungin discontinuation; however, amphotericin B was withdrawn in 5 (29.4%) neonates. None of patients in the caspofungin group had infusion-related adverse events, nephrotoxic effects or hypokalemia requiring potassium supplementation (Table 4).

**Mortality**

Overall four patients died from *Candida* infection: 1 (6.7%) in the caspofungin group and 3 (17.6%) in the amphotericin B group ($p = 0.6$). None of deaths was due to study therapy. Patients were considered to have died from *Candida* infection if any of the following criteria were met: the treating physician identified the *Candida* infection as the cause of death. For all *Candida* species (*albicans* and non-*albicans*), the rate of a favorable response was significantly higher in caspofungin-treated patients (86.7%) than in amphotericin B-treated patients (41.7%, $p = 0.04$). In the caspofungin group, the favorable outcomes were consistent among different forms of fungal infection.

### Table 1

**Clinical characteristics of neonates with invasive candidiasis***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Caspofungin group ($n = 15$)</th>
<th>Amphotericin B group ($n = 17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (week)$^a$</td>
<td>27.9 ± 1.3</td>
<td>28.3 ± 1.1</td>
</tr>
<tr>
<td>Birth weight (g)$^a$</td>
<td>851.0 ± 140.1</td>
<td>901.1 ± 137.2</td>
</tr>
<tr>
<td>Male (%)$^b$</td>
<td>8 (53.3)</td>
<td>10 (58.8)</td>
</tr>
<tr>
<td>Onset of candida infection (day)$^a$</td>
<td>21.1 ± 3.1</td>
<td>22.3 ± 2.4</td>
</tr>
<tr>
<td>Risk factor for invasive candidiasis (%)$^b,c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent use of broad-spectrum antibiotics$^d$</td>
<td>13 (86.7)</td>
<td>15 (88.2)</td>
</tr>
<tr>
<td>Recent use of central venous catheter</td>
<td>2 (13.3)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>1 (6.7)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Recent hyperalimentation</td>
<td>6 (40.0)</td>
<td>8 (47.0)</td>
</tr>
<tr>
<td>Recent use of corticosteroids</td>
<td>5 (33.3)</td>
<td>7 (41.1)</td>
</tr>
<tr>
<td>Preexisting fungal colonization</td>
<td>3 (20.0)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of infection (%)$^b$</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>3 (20.0)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Ventriculitis</td>
<td>1 (6.7)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>5 (33.3)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>2 (13.3)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Urinary candidiasis</td>
<td>3 (20.0)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1 (6.7)</td>
<td>1 (5.9)</td>
</tr>
</tbody>
</table>

$^a$Values are means ± SD.

$^b$Number (%).

$^c$Some patients had more than one risk factor.

$^d$Recent was defined as within 14 days before the study.

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

### Table 2

**Candida isolates***

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Caspofungin group ($n = 15$)</th>
<th>Amphotericin B group ($n = 17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans</em> (%)$^a$</td>
<td>11 (73.3)</td>
<td>13 (76.4)</td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>3 (20.0)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td><em>Candida tropicalis</em></td>
<td>1 (6.7)</td>
<td>2 (11.8)</td>
</tr>
</tbody>
</table>

$^a$Number (%).

*None of the differences between the two groups was statistically significant.

For all *Candida* species (*albicans* and non-*albicans*), the rate of a favorable response was significantly higher in caspofungin-treated patients (86.7%) than in amphotericin B-treated patients (41.7%, $p = 0.04$). In the caspofungin group, the favorable outcomes were consistent among different forms of fungal infection.
Invasive candidiasis is a major cause of morbidity and mortality in neonates, particularly in preterm infants [11]. Invasive candidiasis in neonates may continue to progress despite treatment with conventional amphotericin B [12]. The need for new antifungal agents is likely to increase with a rise in incidence of invasive candidiasis and mycoses coupled with the increasing survival of extreme low birth weight infants [13]. As clinical data have demonstrated that caspofungin is as or more effective and less toxic than deoxycholate amphotericin B in adult patients [14], we speculated that caspofungin was an alternative to deoxycholate amphotericin B in neonates.

To our knowledge, this is the first reported prospective, randomized, double-blind clinical trial which was designed to compare the efficacy and safety of caspofungin with that of amphotericin B.
in neonates with invasive candidiasis although not the first reported use of caspofungin in neonates. The study design and outcome evaluations mirrored those used in prior studies in adult patients [14]. Similarities in design included the clinical and laboratory measurements for safety and the efficacy assessment based on a five-part composite endpoint.

Our results showed that caspofungin was more effective than amphotericin B at the end of intravenous therapy. Also at each evaluation of efficacy, caspofungin was superior to amphotericin B. Differences in efficacy between the two groups were mainly a reflection of treatment failure of amphotericin B due to persistent or recurrent infection. For all various forms of invasive candidiasis as well as all Candida species, the favorable responses to caspofungin were high. Our findings are in accordance with that of Mora et al. [14], in adult patients with invasive candidiasis. The mechanism of action of caspofungin provides a broad spectrum of activity against most fungi [15].

In our study, the incidence of drug-related adverse events in patients treated with caspofungin was generally lower than that in amphotericin B-treated...
neonates. None of the adverse events led to caspofungin withdrawal. None of patients treated with caspofungin had infusion-related adverse events, nephrotoxic effects or hypokalemia requiring potassium supplementation. We did not observe any serious complications that believed to be secondary to caspofungin. Safety of caspofungin was evaluated in a recent comparative empirical therapy study [16]. In this study, drug-related clinical adverse events occurred in 48% of the caspofungin group and 46% of the liposomal amphotericin B group were serious in 2 and 12%, respectively, and required treatment discontinuation in 4 and 12%, respectively.

Safety profile of caspofungin in our patients is consistent with that currently described for pediatric patients [17–20]. Caspofungin appears to manifest a favorable safety profile in newborn infants. Caspofungin inhibits the synthesis of the β-(1,3)-D-glucan component of the fungal cell wall [21]. The absence of β-(1,3)-D-glucan in mammalian cells suggest that the caspofungin should be selectively active against fungal cells and probably contributes to its favorable safety profile [22].

Conclusion

Caspofungin is more effective, safer, appropriate alternative to amphotericin B for the treatment of invasive candidiasis in newborn infants. The main limitation of this study is the total number of patients enrolled which was small; therefore, further studies with larger sample sizes should be undertaken.

References