Liposomal Amphotericin B (AmBisome) in the Treatment of Neonatal Candidiasis in Very Low Birth Weight Infants

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Summary

AmBisome (2.5–7 mg/kg/day as a continuous 1 h infusion) was evaluated prospectively from September 1994 to January 1998 in 24 very low birth weight infants (mean birth weight 847 ± 244 g, mean gestational age 26 weeks) with systemic candidiasis. Mean age at onset of candidemia was 17 days. One patient had two episodes of candidiasis. Thirteen infants failed previous antifungal therapy with amphotericin B (with or without 5-flucytosine). *Candida* spp. were isolated from the blood in all 25 episodes and from skin abscesses and urine in four infants each, respectively. There were 13 isolates of *Candida albicans*, ten of *Candida parapsilosis*, two of *Candida tropicalis* and one of *Candida glabrata*. One infant had a mixed infection with *C. albicans* and *C. parapsilosis*. The mean duration of therapy was 21 days; the cumulative AmBisome dose was 94 mg/kg. Fungal eradication was achieved in 92% of the episodes; mean duration of AmBisome therapy until achieving eradication was 9 days. Twenty (83%) infants were considered clinically cured at the end of treatment. No major adverse effects were recorded; one infant developed increased bilirubin and hepatic transaminases levels during therapy. Four (17%) infants died; in two of them (8%) the cause of death was directly attributed to systemic candidiasis.

Conclusion: AmBisome represents an effective, safe and convenient antifungal agent in the therapy of systemic fungal infections in very low birth weight infants.

Key Words

Liposomal Amphotericin B · Neonates · *Candida*

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Introduction

Systemic candidiasis is reported with increasing frequency in neonates, reaching 16% of cases of late-onset sepsis in the neonatal intensive care unit and 2–4.5% of infants with a birth weight < 1,500 g [1–7]. While *Candida albicans* is the main cause of fungemia, *Candida parapsilosis* has been reported with increased frequency in recent years [7, 8]. Despite major improvements in neonatal care, the mortality rate in neonates with systemic candidiasis receiving the standard of care (amphotericin B with or without 5-flucytosine) continues to be extremely high: 25–54% [1–8].

Amphotericin B is considered by the majority of experts as the treatment of choice for *Candida* infections [9]. However, its use may be limited by adverse effects which include renal toxicity, electrolyte imbalances, hepatotoxicity and bone marrow suppression [9–11]. Fortunately, premature infants appear to experience fewer systemic symptoms (fever, chills, nausea and vomiting) from conventional amphotericin B than adults do [12]. Alternative options for the treatment of neonatal candidiasis are represented by azoles (fluconazole, ketoconazole and itraconazole) and the lipid preparations of amphotericin B. Fluconazole is the only azole used until now in neonates, with confirmed safety and efficacy [9, 13–15]. The resistance of *Candida krusei*, *Candida glabrata* and *Rhodotorula rubra* to fluconazole may limit its use in the treatment of candidiasis [14–16].

Lipid-associated amphotericin B preparations have been developed in order to increase the therapeutic index of the parent compound while maintaining its antifungal activity [17]. AmBisome, the only commercially produced lipid formulation that contains liposomal structures, has been evaluated in large studies performed in adult patients and subsequently has received FDA approval for the treatment of patients with aspergillar, candidal and cryptococcal infections refractory to amphotericin B or in patients intolerant to amphotericin B [17–21]. Recently, AmBisome at either 1 or 3 mg/kg/day was found significantly safer and equivalently or possibly more efficacious than conventional

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amphotericin B for the empirical treatment of presumed fungal infections in immunocompromised children and adults with pyrexia of unknown origin [22].

The purpose of the present study was to investigate the safety profile and obtain preliminary data on the efficacy of AmBisome in the treatment of systemic candidiasis in very low birth weight neonates.

Patients and Methods

This retrospective analysis of prospectively collected data included all the infants treated with AmBisome for an episode of documented systemic candidiasis in the neonatal intensive care units at Kaplan Hospital, Rehovot and Schneider Children's Medical Center, Petach Tikva, Israel, from September 1994 to January 1998. Patients were eligible for enrollment if *Candida* spp. were cultured from blood and urine or cerebrospinal fluid (CSF) with clinical and/or laboratory evidence suggestive of infection or if repeated cultures of the same *Candida* spp. were obtained from one or more sites. Blood (0.5–1 ml) was inoculated into aerobic and anaerobic Bactec radiometric blood culture media (Becton Dickinson, USA) and processed according to standard microbiologic techniques.

We used AmBisome (NeXstar Inc., San Dimas, USA), in a daily dosage of 2.5–7 mg/kg as a continuous 1 h infusion. The initial dosage was 1 mg/kg/day and the dosage was increased stepwise to the desired final dosage in 48–96 h. The final daily dosage was determined by the individual patient's clinical course. Therapy was discontinued if the infants were considered clinically cured and received at least 2 weeks of therapy since the first negative blood culture.

Efficacy evaluations were based on the clinical and mycological responses as recorded in the case report form of the infants. Blood cultures were performed every 24–48 h since initiation of AmBisome therapy. Following the first two negative blood cultures, additional blood cultures were drawn once weekly or according to the clinical status of the patients. Complete blood counts, serum electrolytes and liver function tests were performed before initiation of therapy and at least twice weekly during treatment. All adverse events reported by parents or observed by the investigators were recorded in the case report forms.

Episodes of candidemia were considered different infections in the same patient if they occurred at least 14 days after a documented sterile blood culture.

Candidemia was considered as directly contributory to mortality if death occurred within 7 days of a positive blood culture or if there was autopsy evidence of disseminated candidiasis.

Data is expressed as mean ± SD.

Results

Patients

Details of the cases of the 24 infants with systemic candidiasis are shown in table 1. One patient had two episodes of systemic candidiasis (the first at age 17 days and the second at the age of 100 days). Fourteen (58%) of the infants had a birth weight < 1,000 g. Nine (36%) episodes of systemic candidiasis occurred at < 14 days of age. Thirteen infants failed previous conventional antifungal therapy (amphotericin B alone in four patients and together with 5-flucytosine in nine patients).

The clinical underlying conditions found in our population at the time of the systemic candidiasis episode included respiratory distress syndrome (54%), bronchopulmonary dysplasia (33%) and intraventricular hemorrhage (21%). Nine (38%) of the patients had suffered from an episode of documented bacterial sepsis prior to the present episode of systemic candidiasis. One infant developed *Klebsiella* sepsis, necrotizing enterocolitis and peritonitis on day 15 of AmBisome therapy. Three infants had renal failure (defined as doubling of serum creatinine levels) which developed during therapy with amphotericin B. Another patient had renal failure diagnosed prior to the present episode of systemic candidiasis. Three (13%) infants had necrotizing enterocolitis diagnosed, treated and resolved prior to the present episode of systemic candidiasis. Two patients developed necrotizing enterocolitis while receiving AmBisome treatment. The central catheter was removed in 4/5 infants at the time of diagnosis of systemic candidiasis.

All 25 episodes of systemic candidiasis were associated with clinical symptoms.

Microbiology

Thirteen (53%) *C. albicans*, 10 *C. parapsilosis*, 2 *Candida tropicalis* and 1 *C. glabrata* were isolated. One infant had a mixed infection with both *C. albicans* and *C. parapsilosis*. None of the infants had meningitis, endocarditis or osteomyelitis. In four patients *Candida* was isolated from urine and in another four from skin abscesses in addition to blood. *Candida* was isolated from the tip of the central catheter in 2/3 patients.

AmBisome Treatment

Six infants received the maximal dose of 7 mg/kg/day; five received 6 mg/kg/day and another five were treated with 5 mg/kg/day. Two additonal patients received 4 mg/kg/day and six received 3 mg/kg/day. One infant died after 2 days

Table 1
General data on 24 very low birth weight infants with systemic candidiasis.

Birth weight (mean ± SD)	847 ± 244 g
Range	560 to 1,430 g
Median	826 g
Gestational age (mean)	26 weeks
Range	24–32 weeks
Males/females	10/14
Mean age at onset of candidemia[a]	17 days
Range (25 episodes)	7–100 days
Mean duration of prior amphotericin B therapy (13 infants)	7 days
Range	2–21 days
TPN	25/25 episodes
Prior antibiotic therapy	21/25 episodes
Central vein catheter	5/24 patients

[a] excluding the episode occurring at day 100; TPN: total parenteral nutrition

of therapy while receiving 2.5/mg/kg/day of AmBisome. The mean duration of AmBisome therapy was 21 days (range 2–31 days). The cumulative AmBisome dose was 94 mg/kg (range 4.5 to 139 mg/kg). The mean number of days required until eradication of the pathogen was 9 (range 2 to 18 days). In all, 12/23 infants who completed the treatment needed more than 7 days in order to achieve *Candida* eradication from the blood. Fungal eradication was achieved after means of 9.6 ± 4.8 (range 5–18) days in infants < 1,000 g and 7.4 ± 5.3 (range 2–16) days in infants > 1,000 g. Negative cultures were reported after 12.6 ± 14.3 (median 9.5) days in infants previously treated with amphotericin B (with or without 5-flucytosine) and 9.3 ± 4.5 (median 7) days in neonates who did not receive any antifungal therapy before initiation of AmBisome therapy. No difference was observed in the time required until eradication between the patients with *C. albicans* (9 ± 4.5 days) and to those with *C. parapsilosis* (10 ± 6.1 days) fungemia.

Outcome

Fungal eradication was achieved in 23/25 (92%) episodes. Four (17%) infants died, two of them (8%) due to *Candida* sepsis. The first one died due to persistent *C. parapsilosis* sepsis, with necrotizing enterocolitis and intestinal perforation following 5 days of amphotericin B + 5 flucytosine, 31 days of AmBisome and 5 additional days of AmBisome and fluconazole therapy. The second infant whose death was considered related to *Candida* sepsis received amphotericin B for 4 days followed by only 2 days of AmBisome therapy. He died due to multiple organ failure with repeated blood cultures positive for *C. albicans*. *C. albicans* was recovered from the lungs at postmortem examination.

One of the two infants whose death was considered unrelated to systemic candidiasis died due to necrotizing enterocolitis and *Klebsiella pneumoniae* peritonitis on day 31 of AmBisome therapy after successful eradication of *C. parapsilosis* from blood. The other infant died due to extreme prematurity and severe respiratory distress syndrome following successful eradication of *C. albicans* from blood.

Adverse Effects

None of the patients developed any untoward infusion-related effect of AmBisome severe enough to require symptomatic therapy. A transient increase in serum bilirubin and hepatic transaminases levels was recorded in one infant. None of the infants developed phlebitis, fever or chills during the AmBisome infusion. None of the infants developed hypokalemia (serum potassium < 3.0 mEq/l) during treatment. Renal functions returned to normal during AmBisome therapy in all three infants who developed renal failure during previous amphotericin B treatment.

Discussion

The information about the use of AmBisome in neonates is limited. To date, the use of AmBisome has mainly been limited to infants either failing or having intolerable adverse effects due to conventional amphotericin B and controlled studies comparing AmBisome with other antifungal drugs in use in neonates have not yet been performed. Dosages used have ranged from 1–5 mg/kg/day and no pharmacokinetic studies have been performed.

Lackner et al. [23] reported in 1992 on the successful treatment with AmBisome 5 mg/kg/day of two very low birth weight infants with disseminated fungal infections due to *C. albicans* and *Aspergillus fumigatus*. *Evdouridou* et al. [24] successfully substituted conventional amphotericin B for AmBisome (3.5 mg/kg/day) in a 32-week neonate with fungemia and multifocal osteoarthritis of the lower extremities due to *C. albicans*. In a prospective, uncontrolled study which enrolled 44 neonates (40 preterm infants) with systemic candidiasis, *Scarcella* et al. [25] reported on effective AmBisome therapy in 72.7% patients, including five of six cases with meningitis. The AmBisome dosage used was 4 mg/kg in 95% of the patients; a negative blood culture was obtained after 12.8 days in preterm infants and 4.1 days in full-term infants. The only side effect observed was transient hypokalemia in 36% of the patients. The mortality rate attributed directly to the fungal infection, however, was high (36% of the very low birth weight infants) [25]. *Weitkamp* et al. [26] treated 21 very low birth weight infants with AmBisome (median dose 2.6 mg/kg/day, range 1–5 mg/kg/day) (only seven of them with proven systemic candidiasis) and achieved fungal eradication and clinical recovery in all patients. Fifteen percent of the infants developed hypokalemia during AmBisome treatment, which resolved easily with parenteral potassium supplementation.

Our study population was similar in terms of its main birth parameters and typical risk factors for candidiasis to the previously reported cases of very low birth weight infants treated with AmBisome. However, it is worthwhile mentioning that only five infants had central catheters which were left in place during the amphotericin B therapy and removed (in 4/5 patients) only with the initiation of AmBisome therapy. Our study confirms previous data that AmBisome is a safe and effective drug for use in systemic candidiasis. Fungal eradication was achieved in 92% of episodes, clinical improvement in 83% of the patients and the mortality rate due directly to systemic candidiasis was low (8%). In addition, the lack of response to treatment in one of the infants who succumbed due to systemic candidiasis most probably can be attributed to insufficient AmBisome therapy (only 48 h) which did not reach an effective dosage. Indeed, a previous study reported a shorter duration of therapy and lower mean cumulative AmBisome dosages reached in infants who died with systemic candidiasis than in those who survived, emphazing again that early diagnosis and initiation of therapy is crucial for a successful outcome in this disease [25].

The long period of time required for fungal eradication (9 days while on AmBisome therapy) is puzzling. While previously shown, in a small number of patients, that fungal eradication might be achieved more rapidly in full-term than in preterm infants treated with AmBisome, we could not re-

confirm these findings since all the infants included in our study were premature very low birth weight infants. However, we did observe a more rapid fungal eradication in infants with birth weights between 1,001–1,430 g compared to those < 1,000 g and in those who did not receive any prior antifungal therapy before initiation of AmBisome therapy. These findings suggest that the infants failing conventional antifungal therapies might have a priori a more complicated and more difficult-to-treat disease or, alternatively, AmBisome may indeed be more effective than conventional amphotericin B in the treatment of systemic candidiasis. In addition, we could find no differences in terms of the time required until fungal eradication between infants with *C. albicans* vs infants with *C. parapsilosis* infection.

The AmBisome doses administered in this study were higher than the doses used in neonates in previous studies; a dose of 5–7 mg/kg/day was used in 72% of the 25 episodes. Our study indicates that neonates can be safely managed with daily doses of 5–7 mg/kg/day, although the ideal dosage required for the most effective fungal eradication has yet to be established. While we used a 5–7 mg/kg/day AmBisome dosage in the majority of infants, the therapy was initiated in all cases with a starting dose of 1 mg/kg/day; a higher starting dose (3–5 mg/kg/day) could have possibly achieved earlier fungal eradication.

In conclusion, according to our experience, AmBisome represents an effective, safe and convenient antifungal agent in the therapy of systemic candidiasis in very low birth weight infants. However, experience with this drug has to be extended and pharmacokinetic data on neonates are needed. The definitive and conclusive evidence of its efficacy in the treatment of systemic fungal infections in neonates can be established only from a prospective, randomized, multicenter study comparing AmBisome to conventional amphotericin B or other antifungal agents.

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