SHORT REPORT

Amphotericin B lipid complex for neonatal invasive candidiasis

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Abstract

This study describes the safety and efficacy of amphotericin B lipid complex (ABLC) in 11 neonates with systemic *Candida* infections. Nine of the 11 improved clinically, and eight of nine evaluable patients had a mycological cure with ABLC. Creatinine levels improved or did not significantly change in eight of the 11 patients.

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Disseminated *Candida* infections are becoming increasingly common among infants in intensive care nurseries. Although the treatment of choice has traditionally been amphotericin B, some infants experience nephrotoxicity during treatment, which compromises their ability to complete the treatment. Others fail to respond to conventional doses of amphotericin B and may not tolerate increased doses. Some infants have underlying renal disease or are given other nephrotoxic drugs that can potentiate the nephrotoxicity of amphotericin B.

Although three lipid based amphotericin B products are available in many countries, to date there are few data on their safety and efficacy in neonates. Amphotericin B lipid complex (ABLC) is licensed in the United States for the treatment of invasive fungal infections in adults and children who are refractory to or intolerant of conventional amphotericin B. ABLC is less nephrotoxic at higher concentrations than amphotericin B in animal models and humans.[1] An effective drug that does not have the dose limiting nephrotoxicity of amphotericin B could improve the care of neonates with invasive fungal infections. We report on the open label, emergency use of ABLC in 11 neonates treated before the drug was licensed in the United States. These infants from several institutions were included in previous larger case series[2 3] and represent the largest series of neonates treated with ABLC for whom safety and efficacy have been evaluated.

Methods

Infants were eligible to receive ABLC if they had a culture proven systemic fungal infection and at least one of the following: failure to respond to previous systemic antifungal treatment, acute drug associated nephrotoxicity, and/or underlying renal dysfunction. Informed consent from the parent and/or guardian was obtained before enrollment.

Safety monitoring included the assessment of adverse events and monitoring of renal, hepatic, and haematological variables. The response to treatment was assessed at its completion, and one and four weeks after. The mycological outcome was classified as eradicated in patients with positive pretreatment cultures for *Candida* from one or more normally sterile body sites and negative cultures after treatment. The mycological outcome was considered persistent if the end of treatment culture or the last one obtained remained positive. The mycological outcome was determined to be non-evaluable in patients whose cultures became negative before ABLC, although follow up cultures were obtained to evaluate for sustained eradication or relapse. The clinical outcome was classified as a success if the signs and symptoms of invasive mycosis had resolved or improved at completion of treatment, and a failure if the patient died while receiving ABLC or within 72 hours of completion (regardless of the cause of death), or if clinical signs and symptoms were unchanged or worsened after treatment.

Results

Table 1 shows baseline characteristics for the 11 neonates treated with ABLC. The infants were 3–14 weeks of age (median 7 weeks) and weighed 0.7–5 kg (median 1.4 kg). All had received broad spectrum antibiotics before developing invasive candidiasis. Of the eight premature neonates, all had received corticosteroid treatment, and six had a history of necrotising enterocolitis.

The median duration of ABLC treatment was 23 days (range 4– 41) at an average dose of 4.9 mg/kg/day (range 3.2–6.5). Table 2 shows the clinical and mycological outcomes. Of the nine patients evaluable for mycological response, eight had eradication of infection. Two additional patients with prolonged candidaemia had blood cultures drawn within two days of starting ABLC that were negative. These patients were not evaluable for mycological outcome but had sustained eradication on ABLC. Two patients died during treatment. One infant with histiocytosis and neutropenia died with disseminated candidiasis. The second died of multisystem failure consequent

Table 1 Baseline characteristics for 11 neonates treated with amphotericin B lipid complex (ABLC)

Patient no	Age (weeks)	Weight (kg)	Pre-existing conditions	Site of positive culture	Candida spp.	Reason for ABLC use
1	5	0.7	Prematurity (24 weeks), cardiac and aortic thrombi, NEC	Blood, skin/soft tissue, lung*	*C albicans*	Nephrotoxicity, failure of prior antifungal
2	8	5.0	Intestinal obstruction s/p laparotomy, Hirschsprung's disease	Blood, lung*	*C parapsilosis*	Failure of prior antifungal
3	14	1.4	Prematurity, NEC	Blood	*C tropicalis*	Failure of prior antifungal
4	7	3.5	Transposition of the great vessels s/p repair, renal failure post-op, peritoneal dialysis	Blood, urine, peritoneal fluid	*C albicans*	Nephrotoxicity, failure of prior antifungal
5	3	1.1	Prematurity (26 weeks), NEC, bowel perforation	Blood, urine, peritoneal fluid	*C albicans*	Nephrotoxicity, failure of prior antifungal
6	3	0.8	Prematurity (26 weeks), repair of PDA, NEC, bowel perforation	Blood, urine, peritoneal fluid	*C albicans*	Nephrotoxicity
7	4	3.7	Repair of PDA, chest tube	Blood	*C tropicalis*	Failure of prior antifungal
8	3	2.3	Prematurity, congenital renal dysplasia 2° posterior urethral valves	Skin/soft tissue, urine	*C albicans*	Underlying renal disease
9	8	1.1	Prematurity (26 weeks), NEC, prior candidaemia	Blood	*C parapsilosis*	Failure of prior antifungal
10	7	0.9	Prematurity (23 weeks), NEC, decubiti	Blood, skin/soft tissue	*C parapsilosis*	Failure of prior antifungal
11	8	2.5	Prematurity (32 weeks), Langerhans cell histiocytosis, renal failure, neutropenia	Blood	*C albicans*, *C glabrata*	Underlying renal disease, failure of prior antifungal

*For patients 1 and 2, yeast grew from endotracheal tube aspirates and chest radiographs showed pneumonia. The treating clinician made the diagnosis of *Candida* pneumonia.
NEC, necrotising enterocolitis; PDA, patent ductus arteriosus.

to extreme prematurity, but candidaemia had been eradicated before death. None of the nine patients who survived to complete treatment experienced relapse of infection.

No infant discontinued treatment because of an adverse drug reaction, and none experienced appreciable hepatic or haematological toxicity during treatment. All five infants who were enrolled because of acute nephrotoxicity with amphotericin B tolerated ABLC. Renal function improved or did not change appreciably in eight of the 11 infants. Median pretreatment serum creatinine concentration for the 11 infants was 80 μmol/l (range 35–522 μmol/l) and median end of treatment creatinine concentration was 44 μmol/l (range 18–628 μmol/l) (table 2).

Discussion

ABLC was effective in eradicating *Candida* in neonates who failed to respond to conventional amphotericin B and in those with amphotericin associated nephrotoxicity and/or underlying renal disease. For the three infants who had increased serum creatinine levels after ABLC, it is difficult to determine whether this deterioration was secondary to ABLC, prior renal damage, or use of other nephrotoxic drugs.

ABLC has an improved therapeutic index which allows higher doses to be given with reduced toxicity.[4] As it is associated with lipid, the reduced toxicity may be due to free amphotericin B being restricted from interacting with mammalian cell membranes. Lipases produced by inflammatory cells and fungi may facilitate the release of amphotericin B from the lipid complex directly on to fungal cells.[5] In addition, animal studies show that ABLC concentrations are lower in kidneys than in organs of the reticuloendothelial system—for example, liver and spleen.[6] In studies in adults, patients given ABLC experienced reduced nephrotoxicity compared with those given amphotericin B.[7]

This case series illustrates the potential utility of ABLC as second line treatment in infants with invasive candidiasis who cannot complete a

Table 2 Clinical and mycological outcome and safety of treatment of 11 neonates with amphotericin B lipid complex (ABLC)

Patient no	Prior antifungals	Duration of prior antifungals (days)	Average ABLC dose (mg/kg/day)	Duration of ABLC (days)	Pretreatment creatinine (μmol/l)	Post-treatment creatinine (μmol/l)	Mycological outcome	Clinical outcome
1	Amphotericin 5FC Rifampin	14 10 7	4.7	7	80	97	Eradicated	Failure
2	Amphotericin 5FC	24 24	5.0	23	35	35	NE, ABLC sustained eradication	Success
3	Amphotericin 5FC Rifampin	56 35 18	5.4	14	35	35	NE, ABLC sustained eradication	Success
4	Amphotericin 5FC	13 (QOD) 7	5.0	25	88*	150*	Eradicated	Success
5	Amphotericin	18	6.5	28	88	44	Eradicated	Success
6	Amphotericin 5FC	7 1	3.2	30	141	18	Eradicated	Success
7	Amphotericin	17	4.1	41	44	35	Eradicated	Success
8	Amphotericin	2	4.8	14	522	628	Eradicated	Success
9	Amphotericin 5FC Fluconazole	30 1 12	5.6	17	35	44	Eradicated	Success
10	Amphotericin 5FC	19 12	6.2	29	35	26	Eradicated	Success
11	Amphotericin Fluconazole	1 3	3.9	4	168*	221*	Persisted	Failure

*On dialysis before ABLC treatment.
5FC, 5-Flucytosine; NE, not evaluable; QOD, every other day.

course of conventional amphotericin B. The possible role of ABLC as a first line treatment in this population is not known. Further studies are needed to assess the pharmacokinetics, safety, and efficacy of ABLC in neonates.

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1 Hiemenz JW, Walsh TJ. Lipid formulations of amphotericin B: recent progress and future directions. *Clin Infect Dis* 1996;**22**(suppl):133–44.
2 Walsh TJ, Hiemenz JW, Seibel NL, *et al*. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* 1998;**26**:1383–96.
3 Walsh TJ, Seibel NL, Arndt C, *et al*. Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J* 1999;**18**:702–8.
4 Chopra R, Blair S, Strang J, *et al*. Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients. *J Antimicrob Chemother* 1991;**28**(suppl B):93–104.
5 Swenson CE, Perkins WR, Roberts P, *et al*. In vitro and in vivo antifungal activity of amphotericin B lipid complex: are phospholipases important? *Antimicrob Agents Chemother* 1998;**42**:767–71.
6 Olsen SJ, Swerdel MR, Blue B, *et al*. Tissue distribution of amphotericin B lipid complex in laboratory animals. *J Pharm Pharmacol* 1991;**43**:831–5.
7 Sharkey PK, Graybill JR, Johnson ES, *et al*. Amphotericin B lipid complex compared with amphotericin B in the treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis* 1996;**22**:315–21.