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.

Keywords: Candida; neonate; amphotericin B lipid complex

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. 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 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 candidae mia 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
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 B 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. 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. In addition, animal studies show that ABLC concentrations are lower in kidneys than in organs of the reticuloendothelial system—for example, liver and spleen. In studies in adults, patients given ABLC experienced reduced nephrotoxicity compared with those given amphotericin B. This case series illustrates the potential utility of ABLC as second line treatment in infants with invasive candidiasis who cannot complete a...
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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