SHORT REPORT

Amphotericin B lipid complex for neonatal invasive candidiasis

F Adler-Shohet, H Waskin, J M Lieberman

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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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 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...
NEC, necrotising enterocolitis; PDA, patent ductus arteriosus.

*pFor patients 1 and 2, yeast grew from endotracheal tube aspirates and chest radiographs showed pneumonia. The treating clinician made the diagnosis of Candida albicans.

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

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

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

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

*On dialysis before ABLC treatment.
SFC, 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.

Part of this work was presented at the 36th annual meeting of the Infectious Diseases Society of America, Denver, Colorado, 11–14 November, 1998.

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