Amphotericin B Use in a Community Hospital, with Special Emphasis on Side Effects

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The purpose of this study was to analyze the usage of amphotericin B desoxycholate in a small community hospital, with special emphasis on its side effects and need for premedication. We performed a retrospective chart review for patients who received intravenous amphotericin B from January 1993 to May 1996. Temperature elevation, clinical symptoms during infusion, need for premedication, and fluctuations in serum potassium and creatinine values were especially noted. Statistical analysis showed that toxicity indicated by laboratory values (laboratory toxicity) increased with increasing amphotericin B dose, but clinical side-effects decreased with advancing age. Clinical side effects were not associated with total amphotericin B dosage; laboratory toxicity in our study was not more prevalent in elderly patients. The main finding of this study was that most patients tolerate amphotericin B well and only 23% of patients needed premedication. Our fungal cure rate was 83%. New, expensive preparations of amphotericin B should be reserved for the small subset of patients who either are intolerant of amphotericin B desoxycholate or need high doses for systemic fungal infections.

With the use of broad-spectrum antibiotics, immunosuppression, and long-term intravenous catheters, the incidence of fungemia has risen fivefold to 10-fold in the past 2 decades [1–3]. In spite of the advent of imidazole agents, amphotericin B is still considered the “gold standard” of antifungal therapy [4]. Previous investigators have reported a high incidence of amphotericin B side effects, often in >50% of patients (table 1) [3, 5–12]. Side effects most frequently include chills, fever, and nausea or vomiting, often with renal insufficiency and hypokalemia due to amphotericin B renal tubular damage. In a recent survey of 69 hospitals, 70% of patients were given premedications to prevent amphotericin B side effects [5].

See editorial response by Patterson on pages 339–40.

Because of the toxicity associated with the desoxycholate colloidal form of amphotericin B, several new formulations of amphotericin B complexed with liposomes have been developed, resulting in greater tissue penetration and reduced nephrotoxicity and hypokalemia [13–15]. These expensive new lipid preparations have decreased toxicity, bringing the incidence of chills and fever to as low as 1%–16% and that of nausea and vomiting to only 3%–9%, with virtually no nephrotoxicity [13, 14]. To evaluate adverse effects of conventional amphotericin B as well as the need for premedication, we conducted a retrospective study of amphotericin B use in a small urban community hospital over a 40-month period.

Methods

Straub Hospital is a 152-bed facility in Honolulu where cardiovascular and neurological surgery is performed but not organ transplantation. We reviewed hospital records of patients receiving intravenous amphotericin B from January 1993 until May 1996. Fungal diagnosis, underlying diseases, clinical outcome, and reasons for discontinuing treatment were noted. In addition, both daily and total amphotericin B dosages were recorded. Age, race, and sex were studied as treatment variables; one of the authors (F.P.) examined 95% of these study patients. We noted temperature elevation and symptoms during infusion and use of premedication. Laboratory data were examined for evidence of hypokalemia and renal insufficiency. Hypokalemia was defined as a serum potassium level of <3.5 mg/dL, and renal insufficiency was considered to be a serum creatinine level of ≥1.6 mg/dL with an increase of ≥0.5 mg/dL during amphotericin B therapy.

Outcome for patients with proven fungal infections was evaluated as follows. Cure was defined as eradication of fungus from repeated cultures and resolution of symptoms due to infection. Some patients were considered unevaluable because of a change in antifungal therapy (to azoles) or an insufficient duration of therapy (<5 days). We noted deaths due to fungal infection or other causes. Statistical analysis was done by Pearson’s correlation with the SAS Program (Statistical Analysis System; SAS Institute, Cary, NC). The standard χ² test, Pearson’s χ² test of association, and two-tailed Student’s t-test were also used to determine statistical significance among variables.

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Table 1. Review of data from studies of the toxicity of amphotericin B.

<table>
<thead>
<tr>
<th>Reference (year of study)</th>
<th>No. of patients</th>
<th>Clinical side effects</th>
<th>Hypokalemia</th>
<th>Renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>[6] (1963)</td>
<td>22</td>
<td>78</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>[7] (1962)</td>
<td>6</td>
<td>100</td>
<td>17</td>
<td>83</td>
</tr>
<tr>
<td>[9] (1972)</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>[10] (1990)</td>
<td>50</td>
<td>$&gt;56$</td>
<td>84</td>
<td>60</td>
</tr>
<tr>
<td>[PR] (1997)</td>
<td>102</td>
<td>25</td>
<td>19</td>
<td>15</td>
</tr>
</tbody>
</table>

NOTE. NS = not stated; PR = present report.

Results

During the study period, 102 patients were treated with amphotericin B; nine of these patients were given a repeated course of therapy. Table 2 shows characteristics of this study population. The average total amphotericin B dosage of all patients was 162.5 mg, with a range of 10–840 mg. The average cumulative amphotericin B dose of those cured was 220 mg, vs. 113 mg for patients who were unevaluable or whose treatment failed ($P < .00007$). Patients treated empirically (whose fungal cultures were negative) received an average cumulative dose of only 55 mg. The initial dose of amphotericin B averaged 16 mg, within a range of 1–50 mg. Only six patients had a 1-mg test dose. Mean amphotericin B infusion time was 264 minutes, with a range of 120–600 minutes. The total duration of administration averaged 8.3 days (range, 1–46 days).

As shown in table 2, the majority of patients received amphotericin B for culturally proven fungal infections, rather than as empirical therapy. Most patients had a yeast isolated, either a Candida or Cryptococcus species or, in a few cases, an Aspergillus species. Fungemia, funguria, and yeast respiratory infections were the three most common clinical conditions. Eighty-three percent of patients made a full recovery from documented fungal infections; 16 patients (14.4%) died while receiving amphotericin B treatment; most deaths were due to underlying illnesses. One death was directly attributable to yeast septicemia, and one person died of cryptococcal meningitis and HIV disease. Our average total amphotericin B dose for documented candidal infections was 148 mg, while for aspergillus and cryptococcal infections the average total dose was much higher (294 mg).

Table 3 shows adverse side effects of systemic amphotericin B. No patient experienced anaphylaxis due to amphotericin B.

Table 2. Characteristics of the 102 patients treated with amphotericin B at our facility during the study period.

<table>
<thead>
<tr>
<th>Median age (y)</th>
<th>Mean age (y)</th>
<th>Sex (% male)</th>
<th>Ethnic group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>64</td>
<td>60.4</td>
<td>Reference No. of Clinical Renal</td>
</tr>
<tr>
<td>Pneumonia/ARDS</td>
<td>31</td>
<td>DS</td>
<td>NS 45</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25</td>
<td>Malignancy</td>
<td>23</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14</td>
<td>HIV disease</td>
<td>8</td>
</tr>
</tbody>
</table>

Clinical indication for use (%)

- Fungemia 20
- Empirical therapy (no positive culture) 20
- Funguria 18
- Respiratory infection/colonization 15
- Catheter-tip fungal culture 6
- Esophageal candidiasis 5
- Fungal meningitis 5
- Peritoneal fungal infection 4
- Miscellaneous fungal infection(s) 5

Fungus isolated (%)

- Candida albicans 87
- Cryptococcus neoformans 5.4
- Aspergillus fumigatus 4.5
- Candida tropicalis 1.8
- Candida glabrata 0.9

NOTE. ARDS = acute respiratory distress syndrome.

Fifteen persons required premedication in response to clinical side effects; another 11 patients received “routine” premedication but had no history of amphotericin B side effects. Eighty-one patients did not need any premedication. Twenty-two persons (20%) received diphenylhydramine, 16 (14%) received acetaminophen, 13 (12%) received meperidine hydrochloride, 4 (4%) received hydrocortisone, and none received heparin. In 81% of these cases, multiple premedications were used. As would be expected, 54% of premedicated patients were having clinical side effects, while only 16% of those not premedicated

Table 3. Side effects of amphotericin B in 102 patients.

<table>
<thead>
<tr>
<th>Side effect(s)</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills, fever, and/or nausea</td>
<td>25</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>15</td>
</tr>
<tr>
<td>None</td>
<td>54</td>
</tr>
</tbody>
</table>
experienced fever or rigors with amphotericin B infusion. One person was unable to tolerate amphotericin B because of clinical side effects in spite of premedications; in one additional case, amphotericin B was withdrawn because of nephrotoxicity.

We examined several variables in relation to amphotericin B toxicity. There were no significant sex or race differences in the incidence of clinical or laboratory side effects. In addition, there were no differences in racial compositions among the various age groups. Clinical side effects did not vary significantly with either daily or total amphotericin B doses. Underlying illnesses also did not affect rates of clinical or laboratory toxicities. Of 102 patients in our study, 4 had end-stage renal failure, while an additional 15 patients had preexisting renal insufficiency.

Age was significantly associated with clinical side effects: 48% of patients between ages 22 and 49 years had chills, rigors, and/or nausea, vs. only 19.3% in older age groups (figure 1). There were significant differences in clinical side effects between age groups under and over 50 years by Pearson’s $\chi^2$ test ($P < .0048$). Younger patients were more likely to develop clinical side effects but comprised only 20% of our total treatment group. There were no significant age differences in the incidence of either hypokalemia or nephrotoxicity. As shown in figure 2, both hypokalemia and renal insufficiency were highly correlated with total amphotericin B dosage and number of infusion days. We were unable to assess the effect of infusion time in our retrospective study since most patients were infused over 4–5 hours (94% of all cases).

**Discussion**

Most hospitals in the United States are community based and have fewer than 200 beds. At our small community hospital, intravenous amphotericin B was used fairly frequently; primary use was for yeast fungemia or funguria, and only 20% of patients received amphotericin B empirically because they were immunocompromised. Overall, we had a 83% cure rate for documented infections, which compares favorably with that in other reports [16, 17]. Almost all of our patients were infected with a *Candida* or *Cryptococcus* species; only four were infected with an *Aspergillus* species. Some studies have suggested that a cumulative dosage of 200–400 mg is often sufficient to treat yeast infections; our average total dose of 148 mg for candidal infections was slightly lower.

The major emphasis of our investigation was to study side effects of amphotericin B, which occurred mainly in the younger patients. Most patients did not need premedications, in contrast with the experience of previous authors [11, 18]. In our study, 23% of the patients were premedicated (10% routinely and 13% after previous side effects). In contrast, Grasela et al. reported that in 69 participating hospitals, 70% of patients were medicated prior to amphotericin B infusion [11]. Nicholl et al. premedicated 80% of their patients at Vancouver General Hospital; 85% also received 1-mg initial test doses, with no anaphylactic reactions [18].

We agree with previous reports that found limited usefulness in the initial test dose of amphotericin B [4, 11]. At our institution, we used a test dose only six times (5.4%), and like other investigators, we found that test doses are of little benefit [4, 11].

The incidence of clinical side effects (fever, rigor, and/or nausea) has been reported to be between 14% and 100% in previous studies (table 1). Early studies of amphotericin B comprised mainly patients with endemic dimorphic fungal infections, such as coccidioidomycosis and blastomycosis, requiring prolonged intensive therapy associated with a higher incidence of side effects [5–8]. Later published studies were usually of patients with candidemia, candiduria, or other systemic yeast infections, often treated with short-course therapy [3, 10, 19, 20]. Low-dose amphotericin B use at our institution was associated with a 25% incidence of clinical side effects (table 3), similar to that in other low-dosage studies [3, 9, 11]. Several authors report that large cumulative doses cause increased clinical side effects [6, 8, 21, 22], which may explain

**Figure 1.** Clinical side effects of amphotericin B versus age. $n =$ number of patients in each group.

**Figure 2.** Hypokalemia (*black bars*) and renal insufficiency (*white bars*) versus total dose of amphotericin B. $n =$ number of patients in each group.
the higher incidence of amphotericin B side effects reported in older literature [6–8].

The incidences of nephrotoxicity and hypokalemia in our study were 15% and 19%, respectively. Consistent with previous reports [8, 21, 22], both nephrotoxicity and hypokalemia occurred more often with higher amphotericin B doses (figure 2). As opposed to the clinical toxicity profile, there was no relationship between age and amphotericin B–induced hypokalemia or renal insufficiency. This is in contrast to the finding in a previous study that older patients were more prone to renal damage from amphotericin B [8]. We analyzed our clinical and laboratory side-effect data by racial groups and found no statistically significant differences among these groups. We were unable to find previously published studies that addressed this racial issue.

We were unable to draw any conclusions concerning amphotericin B infusion times, since most patients received this drug over a 4–5-hour period. Short infusions produce higher levels of amphotericin B in the blood [23]. Some authors have found that rapid infusion of amphotericin B (<1 hour) was well tolerated with premedication [22–23], while other authors have shown increased clinical toxicity with rapid infusion [25, 26]. It would be interesting to repeat our study with rapid amphotericin B infusions to see if side effect rates increase, especially in the elderly group.

The clinical side effects of amphotericin B have been partially explained by the release of interleukin-1 [27], prostaglandin E-2 [28], and tumor necrosis factor [29] in response to amphotericin B administration. These experimental findings may help to explain our findings of decreased clinical side effects from amphotericin B in the elderly. It is well documented that cytokine production generally decreases with advancing age [30–33]. This may help to explain why amphotericin causes fewer chills and fever in the elderly. It is also well known that febrile response in the elderly is blunted because of the generally decreased responsiveness of the aging immune system [33, 34].

At our institution, amphotericin B desoxycholate colloidal suspension remains an inexpensive, well tolerated antifungal agent for treatment of systemic yeast infections. Several new liposomal formulations of amphotericin B have been developed that have improved clinical tolerability with decreased nephrotoxicity [13–15]. In our hospital, expensive lipid-complex formulations of amphotericin B are reserved for the small number of patients who cannot tolerate amphotericin B desoxycholate; these new liposomal preparations are also useful for patients who need high doses of amphotericin B for dimorphic fungal infections, such as aspergillosis, phycymycosis, and coccidioidomycosis, primarily to avoid nephrotoxicity. Most patients at our institution were older than age 50 years, and only 20% of these patients exhibited clinical side effects secondary to amphotericin B. This group in particular did not require premedications and tolerated amphotericin B quite well. However, as the total dose of amphotericin B increases, all patients must be monitored closely for both nephrotoxicity and hypokalemia.

In conclusion, for the majority of our patients, amphotericin B can be given cautiously without premedication and at full doses, but the blood pressure must be monitored frequently for the rare occurrence of anaphylaxis. Only when side effects occur should such drugs as meperidine, hydrocortisone, or diphenhydramine be used or the dosage of amphotericin B adjusted. Finally, expensive liposomal amphotericin B preparations are best reserved for select groups of patients intolerant of amphotericin B desoxycholate.

Acknowledgment

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References