Comparative Efficacy of Amphotericin B Colloidal Dispersion and Amphotericin B Deoxycholate Suspension in Treatment of Murine Coccidioidomycosis

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The efficacy of a novel sterol-complexed preparation of amphotericin B, amphotericin B colloidal dispersion, was compared with that of deoxycholate-complexed amphotericin B in an acute murine model of systemic coccidioidomycosis. Mice (CD-1, female) were infected intravenously with 180 or 200 arthroconidia of Coccidioides immitis, and intravenous therapy was begun 3 days later. Six doses in various regimens of either preparation were given over 14 days, and deaths were tallied for an additional 35 days. All regimens that were not acutely lethal prolonged the survival of mice over that of controls (P < 0.001). Quantitative determination of residual burdens of C. immitis in the spleen, liver, and lungs of survivors revealed that the colloidal dispersion was not as effective as the deoxycholate suspension on a milligram-per-kilogram basis. Deoxycholate suspension at 1.3 mg/kg cleared the organs in all mice, whereas colloidal dispersion at 5.0 mg/kg was the lowest dose that cleared organisms from all animals. Lower doses cleared organisms from fewer animals or cleared only selected organs. Deoxycholate suspension was more efficacious than colloidal suspension in clearing C. immitis from the liver or lungs (P < 0.05 to 0.01, dose and organ dependent) at identical doses. No overt toxicity was observed in mice treated with colloidal dispersion at 10 mg/kg. In contrast, deoxycholate suspension at 2.0 mg/kg was acutely toxic; 50% of the treated mice died after treatment. The two complexes were not equivalent on a milligram-per-kilogram basis; the deoxycholate suspension was three to four times more efficacious and also >5- to ≥8-fold more toxic. Thus, the therapeutic index of the colloidal dispersion complex is greater than that of the deoxycholate complex. The amount of amphotericin B per dose could also be increased when given as a colloidal dispersion to an optimally efficacious level. Amphotericin B colloidal dispersion shows promise for the therapy of disseminated coccidioidomycosis and should be tested in other animal models and in humans.

Amphotericin B (AmB) is a broad-spectrum polyene that has been used as the standard therapeutic agent for various mycoses. However, the occurrence of toxic effects, such as irreversible renal damage, limits the doses administered and is a factor in its use (12, 22). Ways to lessen the adverse effects of AmB therapy have been studied in a variety of experimental and human infections. Both chemical derivatization (5, 9, 10) and lipid-based or other carriers (4, 11, 12, 15, 16, 18-22) lessen the toxicity of AmB and allow higher total doses to be administered. However, chemical modification of AmB has been less effective therapeutically, and clinical trials have been abandoned (3, 7). The results of studies on lipid or sterol-based AmB preparations in experimental models and clinical trials against a variety of mycoses have been more encouraging (4, 11, 12, 15, 16, 18-22).

Several physical factors alter the efficacy and associated toxicity of AmB after incorporation into lipid-based carriers (i.e., liposomes). These include the presence or absence of sterols, phospholipid type, lipid ratio, and size of resultant liposomes (8, 11, 18). Experimental and human trials have shown encouraging results for the reduction of toxic effects and improvement of the therapeutic index of AmB when incorporated into phospholipid-based carriers (4, 11, 12, 16, 18-22). However, because some treatment failures have occurred (11, 12, 21), it is apparent that the optimal formulation for lipid-carried AmB remains to be determined.

In the present study, we have tested a novel sterol-based carrier-AmB complex, called AmB colloidal dispersion. AmB colloidal dispersion is made from cholesteryl sulfate and AmB in a 1:1 molar ratio, which forms discoidal complexes of lipid and AmB of about 100 nm in diameter that can be filter sterilized and lyophilized (14). The efficacies of AmB colloidal dispersion and AmB as a deoxycholate suspension were compared in a murine model of acute systemic coccidioidomycosis. Our results indicate that although colloidal dispersion was less efficacious than the deoxycholate suspension on a milligram-per-kilogram basis, significantly higher doses of AmB could be given as a colloidal dispersion and were efficacious with no apparent toxicity.

MATERIALS AND METHODS

Organism. Stock cultures of Coccidioides immitis (strain Silveira) were maintained on 2% glucose-1% yeast extract-2% agar (GYE) slants in the mycelial form at ambient temperature. Arthroconidia were collected in sterile saline from 3- to 4-week-old GYE cultures. Susensions were shaken by hand with glass beads (6-mm diameter) to disperse cell clumps and filtered through several layers of sterile gauze to remove hyphal fragments. The arthroconidia were enumerated by hemacytometer count and diluted in saline to the desired number. Viability was assessed by plate count on GYE.

Inoculation of mice. Six-week-old female CD-1 mice (Charles River Laboratories, Portage, Mich.) were used for
the model of systemic coccidioidomycosis as described previously (1, 2). Two separate experiments were done with randomized groups of 10 mice used in each experiment. In the first experiment, mice (average weight, 22.5 g) were inoculated intravenously (i.v.) with 180 viable arthroconidia in 0.25 ml of saline. In the second experiment, mice (average weight, 20.0 g) were inoculated with 200 viable arthroconidia. These inocula were given to produce mortality of 50% or greater, with no deaths due to infection occurring before day 13 and most deaths occurring between 13 and 20 days postinfection. All mice were provided sterilized food and acidified water ad libitum.

**Therapy regimens.** AmB colloidal dispersion (Liposome Technology, Inc., Menlo Park, Calif.) was supplied as a lyophilized cake and reconstituted with sterile water to a concentration of 5 mg/ml. Dilutions for administration to mice were made in sterile 5% glucose (D5W; Kendall McGaw Laboratories, Inc., Irvine, Calif.). AmB deoxycholate suspension (Fungizone; Bristol-Myers Squibb, Princeton, N.J.) was reconstituted to 5 mg/ml per the manufacturer's instructions and diluted in D5W.

For the first experiment, AmB colloidal dispersion was given at 0.22, 0.66, or 10 mg/kg dose and AmB deoxycholate suspension was given at 0.22, 0.66, or 2.0 mg/kg dose. One group received the buffer used for the AmB colloidal dispersion in an amount equivalent to that in the 10-mg/kg dose and served as the diluent control. One group receiving no therapy served as an untreated control. Six doses of AmB colloidal dispersion at 10 mg/kg had been found to be safe and nontoxic in uninfected mice in preliminary studies (data not shown). Our doses were selected to compare identical doses of both preparations plus a higher dose presumed not to be toxic. In addition, because those preliminary studies had demonstrated no difference in the course of C. immitis infection in mice untreated or treated with the deoxycholate dispersion vehicle (data not shown), a deoxycholate suspension diluent control group was not included. Two groups of mice received six AmB deoxycholate suspension doses intraperitoneally (i.p.) in regimens shown to be safe and efficacious previously (6, 10, 13), at 0.63 and 6.3 mg/kg/dose. One group of mice received the same regimen of deoxycholate suspension diluent control.

The drug regimens used in the second experiment were chosen to better define the comparative efficacies of the two preparations. AmB colloidal dispersion was used at 0.66, 1.3, 2.5, 5.0, or 7.5 mg/kg/dose, and AmB deoxycholate suspension was used at 0.22, 0.66, or 1.3 mg/kg/dose. One group of mice received no therapy. Because AmB colloidal dispersion diluent treatments proved to be no different than no treatments in the initial experiment, no diluent controls were included in the second experiment. In both experiments, therapy was initiated 3 days postinfection. All treatments were given i.v. in 0.1 ml (drug diluted in D5W) on days 3, 5, 7, 10, 12, and 14 postinfection.

Deaths were recorded through 49 days postinfection. At the end of this period, all survivors were killed by cervical dislocation, and necropsy was performed immediately. The spleen, liver, and lungs of each were removed aseptically and weighed. Each organ was homogenized in 5 ml of saline with a Tissuemizer (Tekmar Co., Cincinnati, Ohio), and dilutions of the homogenates were plated for determination of the number of viable CFU of C. immitis. Residual burdens of C. immitis in the organs were expressed as the log_{10} CFU per organ.

**Statistics.** Differences in the cumulative mortalities of the various therapy groups in each experiment were analyzed by the Wilcoxon rank sum test, and organ burdens were analyzed by the Mann-Whitney U statistic (17). For the analysis of organ burdens, a value of 7 log_{10} CFU per organ was assigned to missing datum points (due to death of the animals). This value represents the approximate number of CFU in each organ just prior to death and was established from prior studies. This assignment also ensures that, in nonparametric rank tests, death is designated as a worse outcome than is survival with any amount of residual infection.

**RESULTS**

**Experiment 1.** The cumulative mortality of mice in the various therapy groups infected with 180 arthroconidia of C. immitis is shown in Fig. 1. Most deaths occurred between days 13 and 20 postinfection. By day 49, 70% (7 of 10) in both the untreated control and colloidal dispersion buffer-treated groups had died (Fig. 1). No mice treated with AmB colloidal dispersion at the 10-mg/kg dose or with AmB deoxycholate suspension at the 0.22- or 0.66-mg/kg dose died during the 49-day assay (Fig. 1). However, 10% (1 of 10) of the mice treated with AmB colloidal dispersion at 0.22 or 0.66 mg/kg died. In the group of infected mice treated i.v. with the 2.0-mg/kg dose of AmB deoxycholate suspension, 50% (5 of 10) died during the first week of therapy. These deaths occurred immediately (<1 h) after a dose and were attributed to acute toxicity rather than to infection. Except for the mice treated with the AmB deoxycholate suspension at 2.0 mg/kg/dose, all other therapy regimens with either preparation prolonged survival (P < 0.01) over that of either control group.

Table 1 presents the results of the enumeration of the residual burdens of C. immitis in the spleen, liver, and lungs of all surviving mice from the first experiment. All organs in untreated and colloidal dispersion buffer-treated control mice harbored a mean 4 to 5 log_{10} CFU of C. immitis per organ (Table 1). All mice (10 of 10) treated with AmB colloidal dispersion at 10 mg/kg/dose were free of residual infection in all three organs, whereas only 50% (5 of 10) of those treated with AmB deoxycholate suspension at 0.66 mg/kg/dose harbored no C. immitis (Table 1). No C. immitis was recovered from the organs of the five surviving mice treated with AmB colloidal dispersion at the 10 mg/kg dose.
TABLE 1. Recovery of C. immitis from the organs of surviving mice in experiment 1

<table>
<thead>
<tr>
<th>Treatment group and dose (mg/kg)</th>
<th>No. of survivors&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of survivors with organisms cleared from:</th>
<th>Organ burden (mean log&lt;sub&gt;10&lt;/sub&gt; CFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spleen</td>
<td>Liver</td>
</tr>
<tr>
<td>Untreated control</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AmB colloidal suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diluent control</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treated groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.22 mg/kg/dose</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.66 mg/kg/dose</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2.0 mg/kg/dose</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>AmB deoxycholate suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.22 mg/kg/dose</td>
<td>10</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>0.66 mg/kg/dose</td>
<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>2.0 mg/kg/dose</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ten mice per group.
<sup>b</sup> No C. immitis recovered from the organs of 10 mice.
<sup>c</sup> No C. immitis recovered from the organs of five mice.
<sup>d</sup> Five mice died due to acute toxicity, and no C. immitis was recovered from the organs of the five surviving mice.

which had received AmB deoxycholate suspension at 2.0 mg/kg/dose i.v.; five mice in this group died of acute toxicity during the first week of therapy. However, on necropsy, all of these survivors were noted to have partial kidney atrophy and possible liver damage, as evidenced by capsular pallenness. All mice that had been treated with AmB deoxycholate suspension at 0.22 mg/kg/dose or with AmB colloidal dispersion at 0.22 or 0.66 mg/kg/dose harbored residual infection in one or more organs (Table 1).

The residual burdens of C. immitis in the organs of mice in both control groups were equivalent (P > 0.05). Mice treated with AmB colloidal dispersion at 0.22, 0.66, or 10 mg/kg/dose or with AmB deoxycholate suspension at 0.22 or 0.66 mg/kg/dose carried significantly lower residual burdens of C. immitis than did any control group (P < 0.001 for all organs). Compared with mice treated with the 10-mg/kg dose of AmB colloidal dispersion, more organisms were recovered from mice given the 0.22- or 0.66-mg/kg dose of AmB colloidal dispersion (P < 0.001 for all organs) as well as from mice given the 0.22- or 0.66-mg/kg dose of AmB deoxycholate suspension (P < 0.001 to 0.05, depending on the organ).

Mice treated with the 0.66-mg/kg dose of AmB deoxycholate suspension had lower residual burdens of C. immitis than did mice treated with the 0.66-mg/kg dose of AmB colloidal dispersion (P < 0.01 for liver or lungs, P < 0.05 for spleen). This was also true for both preparations with the 0.22-mg/kg dose treatments with respect to the spleen and lungs (P < 0.05) but not the livers (P > 0.05).

The two i.p. AmB deoxycholate suspension regimens also resulted in 100% survival (data not shown). The 0.63-mg/kg dose gave results similar to those with the 0.66-mg/kg i.v. dose (mean log<sub>10</sub> CFU in spleen, liver, and lung were 0.3, 3.1, and 1.1, respectively), and the 6.3-mg/kg dose conferred no marked advantage (0.7, 1.9, and 1.0 log<sub>10</sub> CFU, respectively). Of the 10 mice in each group, only 1 and 2, respectively, were completely cleared of infection. The i.p. diluent control group had the same results as the untreated group.

Experiment 2. Figure 2 presents the cumulative mortality of mice in the various therapy groups infected with 200 arthroconidia of C. immitis. All mice on any regimen with either preparation survived throughout the assay period. All untreated control mice died between days 14 and 23 postinfection (Fig. 2). All drug regimens significantly prolonged the survival of infected mice over that of controls (P < 0.001). No differences in survival occurred between drug regimens.

Table 2 presents the results of the determination of the residual organ burdens of C. immitis from surviving mice in the second experiment. No untreated control mice survived through the 49-day experiment, and thus no quantitative counts were done. All mice that had been given AmB colloidal dispersion at 5.0 or 7.5 mg/kg/dose or AmB deoxycholate suspension at 1.3 mg/kg/dose were free of detectable C. immitis in all three organs cultured (Table 2). Three mice that had received AmB deoxycholate suspension at 0.66 mg/kg/dose and one and four mice given AmB colloidal dispersion at 1.3 and 2.5 mg/kg/dose, respectively, harbored no residual C. immitis in the organs assayed (Table 2). All remaining mice harbored residual C. immitis in one or more organs (Table 2).

Comparisons of the residual organ burdens of C. immitis indicated that all regimens significantly lowered the burdens over those estimated for untreated controls (P < 0.001; see explanation of statistical analysis in Materials and Methods). Groups that had received AmB colloidal dispersion at 5.0 or
7.5 mg/kg/dose or AmB deoxycholate suspension at 1.3 mg/kg/dose were not different \( (P > 0.05) \). Comparison of these three regimens with others indicated that they were superior to regimens with AmB colloidal dispersion at 2.5 mg/kg/dose in the liver \( (P < 0.05) \), at 1.3 mg/kg/dose in the liver and lung \( (P < 0.001 \) and \( P < 0.005 \), respectively), and in all organs of mice at 0.66 mg/kg/dose (spleen, \( P < 0.05 \); liver and lung, \( P < 0.001) \). The three treatments also were superior to AmB deoxycholate suspension in reducing liver burdens at the 0.66-mg/kg dose \( (P < 0.005) \) and in reducing liver and lung burdens at the 0.22-mg/kg dose \( (P < 0.001 \) for both organs). As in the first experiment, mice given a nontoxic dose of AmB deoxycholate suspension carried lower burdens of \( C. \) immitis in one or more organs than did mice given an equivalent dose of AmB colloidal dispersion.

**DISCUSSION**

In the present investigation, the efficacy of two AmB preparations was compared for the treatment of systemic murine coccidiodomycosis. AmB colloidal dispersion was well tolerated, with treated animals showing no overt signs of acute or chronic toxic effects during or after six 10-mg/kg doses, the highest dose tested. No changes in kidney size or appearance were noted on gross examination at the end of the experiments. In contrast, AmB deoxycholate suspension at a dose of 2.0 mg/kg was acutely toxic. Drug-related mortality, presumably due to cardiorespiratory arrest, was observed in 50% of mice given this dose regimen. These deaths were acute, occurring within 1 h or less after a dose was administered. Interestingly, 50% of the mice survived the six doses given. However, these survivors had some tissue damage when examined on necropsy. These results are comparable to those with doses of AmB that induce lethal toxicity in mice that have been reported by other investigators \( (4, 9, 18) \). In addition, similar to the reduction of toxicity of AmB by intercalation into lipid-based carriers reported in several studies \( (4, 11, 15, 18-20) \), the colloidal dispersion displayed reduced toxicity. Because the 1.3-mg/kg dose of AmB deoxycholate suspension was the highest dose that was not overtly toxic in our study, whereas 2.0 mg/kg was a toxic dose, we estimate that the AmB colloidal dispersion preparation reduced the toxicity of AmB by \( >5 \) to \( >8 \)-fold, thus improving the therapeutic index. However, this aspect should be studied further with higher doses of AmB colloidal dispersion and by comparing glomerular filtration indices after treatment with the two preparations.

Both AmB preparations significantly prolonged the survival of mice infected with \( C. \) immitis. Equivalent nontoxic dose regimens of these AmB preparations showed equal efficacy in prolonging survival in these studies. However, comparison of the residual organ burdens of \( C. \) immitis in treated mice showed that they are not equivalent on a milligram-per-kilogram basis. While AmB colloidal dispersion regimens of 5.0, 7.5, or 10.0 mg/kg/dose cleared \( C. \) immitis from the spleen, liver, and lungs of all mice, lower doses cleared infection from fewer mice or only from selected organs. Equal nontoxic regimens of AmB deoxycholate suspension were more effective in eradicating residual burdens of \( C. \) immitis. An AmB deoxycholate suspension dose of 1.3 mg/kg cleared the organs of \( C. \) immitis in 100% of mice, whereas the equivalent dose of AmB colloidal dispersion cleared all three organs in only 10% of the mice. Similar results were observed at doses of 0.66 mg/kg for both preparations. Thus, from these data, we estimate that AmB deoxycholate suspension is fourfold more active than AmB colloidal dispersion, comparing nontoxic doses of each drug that effect complete eradication of \( C. \) immitis from the organs examined. Alternatively, at less-effective doses, equivalence could be estimated by the results in experiment 1 with AmB deoxycholate suspension at 0.22 mg/kg/dose and AmB colloidal dispersion at 0.66 mg/kg/dose (a threefold difference in dose) and in experiment 2 with the former at 0.66 mg/kg/dose and the latter at 2.5 mg/kg/dose (a fourfold difference in dose).

Our studies did not address the question of tissue distribution. However, we noted that in mice treated with nearly effective doses of either preparation, any residual burden of \( C. \) immitis was most often found in the liver. In these studies, the rank order of organ clearance of \( C. \) immitis was, in general, spleen > lungs > liver, with the liver being the most difficult organ to clear. These data might be an indica-

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**TABLE 2. Recovery of \( C. \) immitis from the organs of surviving mice in experiment 2**

<table>
<thead>
<tr>
<th>Treatment group and dose (mg/kg)</th>
<th>No. of survivors*</th>
<th>No. of survivors with organisms cleared from:</th>
<th>Organ burden (mean ( \log_{10} ) CFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AmB colloidal dispersion</td>
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</tr>
<tr>
<td>Treated groups</td>
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<td>0.66</td>
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<td>2.90</td>
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<tr>
<td>2.5*</td>
<td>10</td>
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<tr>
<td>5.0*</td>
<td>9</td>
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<td>0.59</td>
</tr>
<tr>
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<td>10</td>
<td>9</td>
<td>0.28</td>
</tr>
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<td>1.3*</td>
<td>10</td>
<td>10, 10, 10</td>
<td>1.88</td>
</tr>
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</table>

* Ten mice per group except for AmB colloidal dispersion at 5.0 mg/kg (nine mice in the group).

* No \( C. \) immitis recovered from the organs of one mouse.

* No \( C. \) immitis recovered from the organs of four mice.

* No \( C. \) immitis recovered from the organs of the surviving mice.

* No \( C. \) immitis recovered from the organs of three mice.
tion that the tissue distribution of both preparations in mice infected with *C. immitis* is similar.

Several studies have been done with different phospholipid-based carriers for AmB. Hopfer et al. (8) demonstrated that the presence of ergosterol or cholesterol in the phospholipid preparation significantly increased the concentration of AmB required to kill 18 of 19 yeasts in vitro. Szoka et al. (18) showed that lipid composition, molar ratio of lipid, and physical size of the liposome greatly affected the cytotoxicity of AmB for a cultured murine cell line as well as lethality for mice. No correlation between cytotoxicity and lethality could be made, nor were the formulations studied different in fungicidal activity against two yeasts in vitro (18). Furthermore, these authors showed that small unilamellar sterol-containing vesicles reduced AmB toxicity to a greater degree than did larger-sized vesicles (18).

Experimental and human trials have shown that the incorporation of AmB into lipid-based carriers greatly reduces adverse reactions and improves the therapeutic index (4, 11, 12, 15, 16, 19–22). However, some treatment failures have occurred in the human trials (11, 12, 21). Although the optimal formulation remains to be determined, the use of biocompatible lipid-based carriers remains a useful method to reduce toxicity and increase the therapeutic index of AmB. Most of these studies used preparations containing a mixture of lipids and a high lipid-to-AmB ratio (4, 11, 12, 19–22). Patterson et al. (15) tested a complex of AmB-cholesterol sulfate similar to AmB colloidal dispersion (14). In a rabbit model of aspergillosis, they found that AmB was more effective than the AmB-cholesterol sulfate complex when given at equivalent doses (15). However, the reduction of toxicity with the complexed AmB allowed administration of doses that sterilized Aspergillus fumigatus infection in the organs, whereas nontoxic doses of AmB did not eradicate the infection (15). Our results are in accord with theirs and further indicate that preparations such as AmB colloidal dispersion are efficacious.

In summary, AmB colloidal dispersion was found to be safe and efficacious against systemic murine coccidioidomycosis. It is three- to fourfold less active than AmB deoxylate cholate suspension on a milligram-per-kilogram basis, comparing doses equivalent in the ability to clear residual organism burdens in organs. However, AmB colloidal dispersion was >5 to ≥8-fold less toxic. This overall reduction in acute and chronic toxicities compensates for the lower efficacy in vivo, allowing the total dose of AmB to be increased to efficacious levels as well as improving the therapeutic index of AmB. This experimental preparation shows great promise for the treatment of refractory mycoses and should be studied further in both additional animal models of other mycoses and preliminary human trials.

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REFERENCES


