Amphotericin B Lipid Complex Therapy of Experimental Fungal Infections in Mice

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The amphotericin B lipid complex (ABLC), which is composed of amphotericin B and the phospholipids dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol, was evaluated for its acute toxicity in mice and for its efficacy in mice infected with a variety of fungal pathogens. ABLC was markedly less toxic to mice when it was administered intravenously; it had a 50% lethal dose of >40 mg/kg compared with a 50% lethal dose of 3 mg/kg for Fungizone, the deoxycholate form of amphotericin B. ABLC was efficacious against systemic infections in mice caused by Candida albicans, Candida species other than C. albicans, Cryptococcus neoformans, and Histoplasma capsulatum. ABLC was also efficacious in immunocompromised animals infected with C. albicans, Aspergillus fumigatus, and H. capsulatum. Against some infections, the efficacy of ABLC was comparable to that of Fungizone, while against other infections Fungizone was two- to fourfold more effective than ABLC. Against several infections, Fungizone could not be given at therapeutic levels because of intravenous toxicity. ABLC, with its reduced toxicity, could be administered at drug levels capable of giving a therapeutic response. ABLC should be of value in the treatment of severe fungal infections in humans.

Opportunistic infections caused by fungi are one of the leading causes of death in immunocompromised individuals, such as cancer patients undergoing chemotherapy, patients with immunological disorders, transplant recipients on immunosuppressive therapy, or individuals with human immuno deficiency virus infections (6, 26). The polyene macrolide antibiotic amphotericin B (AmB) remains the drug of choice for treatment of these severe life-threatening infections (26), despite a narrow therapeutic index which limits the amount of AmB which can be given.

Lopez-Berestein and coworkers have used liposomes made of dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), and AmB for therapy of systemic fungal infections in experimental animals (15, 16) and humans (12–14, 25). These liposomal AmB preparations have reduced toxicity in experimental animals and exhibit efficacy equivalent to that of Fungizone, the deoxycholate formulation of AmB. Lopez-Berestein and colleagues, using this liposome formulation, have successfully treated patients with systemic Candida infections (14), hepatosplenic candidiasis (12), and Aspergillus infections (12, 14). In a review of 46 patients who underwent liposomal AmB therapy, Lopez-Berestein et al. (12) reported that 25 of 46 patients with a variety of fungal infections were classified as complete responders following liposomal therapy.

Other investigators have used a variety of liposomal formulations of AmB to successfully treat experimental Candida (1, 3, 7, 23), Histoplasma (21), and Cryptococcus (4) infections in mice. All of these studies demonstrated that incorporation of AmB into liposomes improved the therapeutic index. Patterson et al. (18), in a departure from liposomal formulations, used AmB-cholesterol sulfate complexes to treat aspergillosis in rabbits. Kirsh and coworkers (10), in another novel approach, reported that production of an emulsion with AmB and Intralipid reduced the toxicity of AmB while retaining its efficacy against experimental murine candidiasis.

Sculier et al. (21) have also successfully treated patients with their AmB-liposome preparation, which they termed ampholiposomes. Their results are in agreement with those of Lopez-Berestein et al. (12–14), because the toxic manifestations connected with AmB therapy were reduced and significant clinical improvement was noted in some patients. It is evident that incorporation of AmB into lipid structures can reduce the toxicity of the polyene antibiotic while maintaining its efficacy. The liposomal studies described above used different lipids, including the presence or absence of sterols and particles of different sizes. Thus, it is difficult to compare the relative toxicities and efficacies of the different preparations.

Using DMPC and DMPG as used by Lopez-Berestein, Jannof et al. (8) increased the content of AmB over that used by Lopez-Berestein et al. (16) and reported the formation of unusual lipid structures or aggregates of lipid and AmB. These aggregates were not true liposomes but were AmB lipid complexes (ABLCs). We investigated the biological characteristics of ABLCs in experimental animals. The toxicity of ABLC in mice was reduced compared with that of Fungizone, and ABLCs were efficacious against a variety of systemic fungal infections in mice, comparing favorably with Fungizone and the other antifungal agents used in this study. With their efficacy and reduced toxicity, ABLCs may be of value in the therapy of serious fungal infections in humans.

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MATERIALS AND METHODS

ABLC and other antifungal drugs. ABLC was obtained from The Liposome Co., Princeton, N.J. The complex consisted of DMPC and DMPG in a 7:3 molar ratio, with AmB used at a concentration of 33 mol%. The particulate

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preparation had a particle size of 1.6 to 11.1 μm, with 90% of the particles being between 1.6 and 6 μm. All dilutions of ABLC were made in 0.9% sodium chloride for intravenous administration. Fungizone, intravenous (Bristol-Myers Squibb, Princeton, N.J.), was diluted in 5% glucose for intravenous administration. Fluconazole (Pfizer, Groton, Conn.) was dissolved in distilled water, iraconazole (Jansen Pharmaceutica, Piscataway, N.J.) was solubilized in 200-molecular-weight polyethylene glycol, and ketoconazole (Jansen) was placed in 5% dimethyl sulfoxide in 5% carboxymethyl cellulose. Fluconazole, iraconazole, and ketoconazole were administered per os.

**AmB assay procedure.** AmB was analyzed by high-performance liquid chromatography (HPLC). The HPLC components included two M6000 pumps and a model 660 solvent controller (Waters Associates, Milford, Mass.) and an ISS-100 autosampler, an LC75 detector, and an LCI-100 computing integrator (Perkin-Elmer, Norwalk, Conn.). AmB was detected at a wavelength of 405 nm. A C18, 5-μm column (4 by 250 mm; Nicolet Instruments, Madison, Wis.) with a C18 Guard-Pak precolumn module (Waters Associates) was used for the analysis. The mobile phase was methanol (80%; EM Industries, Gibbstown, N.J.) and 0.005 M dipotassium EDTA (20%; Sigma Chemical Co., St. Louis, Mo.) run at a flow rate of 2.0 ml/min. The AmB standard was prepared from Squibb House Standard (SQ 9468; lot AmpoB-6) in dimethyl sulfoxide-methanol and was added to mouse plasma. The spiked plasma was extracted with 3 volumes of methanol (1:1) for use as an external standard for assay calibration. The minimum detectable levels of AmB in this system were 0.4 μg/ml in plasma and 2.0 μg/ml in tissue.

**Animals.** Female Swiss Webster mice (weight, 20 to 25 g at the initiation of each study; Taconic Farms, Germantown, N.Y.) were used.

**Acute toxicity.** Groups of five mice each were administered ABLC or Fungizone intravenously via a lateral tail vein. Animals were observed for 7 days, at which time the surviving animals were sacrificed. Animals were challenged with 10, 20, 30, and 40 mg of ABLC per kg of body weight and with 1, 2.5, 5, and 10 mg of Fungizone per kg of body weight.

**Pharmacokinetic studies in mice.** AmB was administered intravenously to mice as ABLC at 10 and 1 mg/kg or as Fungizone at 1 mg/kg. Blood and tissue samples were collected for analysis at 1, 6, and 24 h after drug administration. Plasma was extracted with methanol (1:4) and centrifuged for 3 min at 20,000 × g, and the supernatant was analyzed by HPLC. Brains, lungs, livers, spleens, and kidneys from three mice were pooled, weighed, and homogenized in water (4 ml of water added per gram of tissue). The homogenates were extracted with methanol (1:4), centrifuged, and analyzed by HPLC.

**Model infections.** (i) **Candida infections.** Organisms were maintained on Sabouraud dextrose agar at 25°C. Molds were incubated 3 to 4 weeks and sporulated. Spores were harvested by washing the plates with sterile distilled water and washed twice with distilled water, and the number of spores per milliliter was determined by a hemocytometer. Four plates indicated that the spore suspension was over 95% viable.

To ensure a uniformly lethal infection in mice, animals were immunosuppressed with one subcutaneous injection of 1.25 mg of triacylchlorine acetone (Kenalog; Bristol-Myers Squibb) per mouse 3 days prior to infection. Mice were infected by intravenous injection of 10⁵ or 10⁶ spores contained in 0.2 ml of saline. Therapy was initiated at 5 h postinfection and given once a day for 7 consecutive days.

ABLC and Fungizone were given intravenously, and fluconazole and itraconazole were given orally. Surviving animals were sacrificed at the end of each experiment (21 to 28 days), and their kidneys and lungs were cultured for the presence of viable *A. fumigatus* by homogenization in distilled water and plating the homogenate on Sabouraud dextrose agar. As in the case of *Candida* infections, ED₅₀'s were based on survival and clearance of the infecting organisms from the cultured organs. Any organism homogenate with 10² or more CFU was counted as positive for *A. fumigatus*.

(ii) **Aspergillus infections.** *Aspergillus fumigatus* was grown on Sabouraud dextrose agar plates. Spores were harvested by washing the plates with sterile distilled water and washed twice with distilled water, and the number of spores per milliliter was determined by a hemocytometer. Four plates indicated that the spore suspension was over 95% viable.

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(iii) **Cryptococcus infections.** A clinical isolate of *Cryptococcus neoformans* was grown in BHI broth for 48 h at 28°C with gentle agitation. Cells were harvested by centrifugation and resuspended in saline for use. Each mouse was infected
intravenously with $2 \times 10^5$ CFU contained in 0.2 ml of saline. Treatment with the antifungal preparations was begun 2 days after infection and was continued once a day for 7 consecutive days. ABLC and Fungizone were given intravenously, and fluconazole and itraconazole were given orally. Surviving animals were sacrificed at 31 days. Brains and lungs were removed, homogenized in distilled water, and cultured in BHI agar. ED$_{50}$s were based on survival and clearance of cryptococci from cultured brains and lungs. For calculation of clearance ED$_{50}$s, any lung or brain homogenate with more than $10^3$ CFU was counted as positive for C. neoformans.

(iv) *Histoplasma* infections. *Histoplasma capsulatum* was grown in BHI broth at 37°C for 48 h. Cells were harvested by centrifugation, washed twice with saline, and counted in a hemacytometer. Mice were infected by the intravenous injection of $5 \times 10^7$ yeast cells, and treatment was initiated 3 days later. Animals were treated once a day for 5 consecutive days. ABLC and Fungizone were given intravenously, and the other agents were given orally. Efficacy was determined by survival for 6 weeks following infection.

The efficacy of ABLC was also determined in immunosuppressed mice with *Histoplasma* infections. Mice were immunosuppressed by the subcutaneous injection of 1.25 mg of trimacinolone acetonide per mouse 3 days before challenge. Animals were infected with $5 \times 10^7$ *H. capsulatum* cells. Therapy was initiated 3 days later and was continued for 5 consecutive days, as in the case of normal animals infected with *H. capsulatum*. Efficacy was determined by survival for 6 weeks following infection.

**RESULTS**

**Acute toxicity in mice.** The acute toxicity of ABLC compared with that of Fungizone was determined by one intravenous injection of the two preparations into mice. The 50% lethal dose (LD$_{50}$) of ABLC under these conditions was $>40$ mg/kg, compared with an LD$_{50}$ of 3 mg/kg for Fungizone. LD$_{50}$s were calculated by the method of Reed and Muench (20). The acute LD$_{50}$ of ABLC was $>40$ mg/kg in over 10 separate experiments with ABLC. If an ABLC-injected animal died, it was usually 24 to 48 h after challenge at the highest dose used (40 mg/kg). At this time the animal lost weight and was noticeably stressed. Animals that died after receiving intermediate levels of Fungizone (2 to 4 mg/kg) had the same stressed appearance and usually died within the same periods; as did the occasional animal challenged with 40 mg of ABLC per kg. Animals challenged with 10 mg of Fungizone per kg died within minutes.

The safety of ABLC was further noted in a study carried out to determine tissue distribution after repeat dosing (data not shown). Mice received 10 mg of ABLC per kg intravenously daily for 14 consecutive days. At the termination of the study, all animals appeared normal. Levels of serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, blood urea nitrogen, and creatinine in plasma were all within normal limits.

**Plasma and tissue distribution.** The levels in tissue and plasma following a single intravenous injection of ABLC or Fungizone are presented in Table 1. Concentrations of AmB in plasma tended to be lower for ABLC when a dose equivalent to that of Fungizone was given. There was no dose proportional increase in the concentrations of AmB in the plasma of animals injected with 1 to 10 mg of ABLC per kg. AmB concentrations in tissue following ABLC administration were highest in livers, spleens, and lungs, organs which are part of the reticuloendothelial system. This was expected, in view of the particulate nature of ABLC (19). Dose-dependent increases in AmB concentrations were seen in reticuloendothelial system organs after ABLC injection. It should be noted that even though lungs and spleens contained a significant amount of AmB in terms of micrograms of AmB per gram of tissue following intravenous ABLC injection, the liver was the major site of AmB deposition, with 49% of the administered dose recovered at 6 h in animals receiving 1 mg of ABLC per kg. AmB in spleens (3%) and lungs (4%) accounted for only a small percentage of the administered dose of ABLC because their small sizes relative to that of the liver.

**Efficacy against *Candida* infections.** The efficacy of ABLC was determined in mice infected with $10^5$ cells of four different clinical isolates of *C. albicans*. Therapy with the appropriate antifungal agent was given once a day for 7 consecutive days starting on the second day of infection. Both ABLC and Fungizone were very efficacious against these infections based on survival (Fig. 1).

ED$_{50}$s based on survival ranged from 0.05 to 0.3 mg/kg/day for ABLC and from 0.07 to 0.4 mg/kg/day for Fungizone in infections involving four different *C. albicans* isolates (Table 2). Based on kidney clearance, ABLC ED$_{50}$s ranged from 0.6 to $>3.2$ mg/kg/day, compared with Fungizone, the ED$_{50}$ of which ranged from 0.2 to $>0.8$ mg/kg/day. It should be noted that Fungizone cannot be given intravenously to infected mice on a daily schedule at doses higher than 0.8 mg/kg. This level of Fungizone can be considered the maximum tolerated dose.

The in vitro activity of ABLC was very similar to that of AmB. In an agar dilution procedure with 10 different strains of *C. albicans*, ABLC MICs ranged from 0.1 to 0.2 μg/ml, on the basis of AmB content, compared with 0.2 μg/ml for AmB alone. By a broth dilution procedure, ABLC gave a MIC of
0.4 μg/ml and a minimum fungicidal concentration of 0.8 μg/ml against a C. tropicalis isolate, compared with a MIC of 0.4 μg/ml and a minimum fungicidal concentration of 0.4 μg/ml for AmB.

There was no toxic reaction to the highest dose of ABLC used in these studies (3.2 mg/kg). For example, for C. albicans SC 5314 infection, 10 of 10 animals in the 3.2-mg/kg group survived, and 9 of the 10 animals had no detectable C. albicans in their kidneys.

ABLC and Fungizone were evaluated for their efficacies in a cyclophosphamide-induced leukopenic mouse model of systemic candidiasis. The response of the infected mice to ABLC and Fungizone therapy was very similar, as noted in Table 2. All infection control animals were dead by 12 days.

The effectiveness of ABLC in treating infections caused by non-C. albicans species of Candida was determined in mice infected with C. tropicalis, C. guilliermondii, or C. stellatoidea. ABLC and Fungizone were efficacious against all of these infections when prolonged survival was considered (Table 3). ABLC treatment achieved kidney clearance with 2 of the 3 non-C. albicans isolates, whereas Fungizone could not be given at high enough levels.

**Aspergillus infections.** Mice immunosuppressed with trimcinolone were challenged intravenously with 10⁵ or 10⁶ spores of A. fumigatus. Therapy was initiated 5 h after infection and was continued once a day for 7 days (Table 4). Against the infection induced by 10⁵ spores, ABLC and Fungizone were both effective in terms of prolonging survival. In this model, ABLC was given at a top dose of 12.8 mg/kg with no evident toxic manifestations. In animals challenged with 10⁶ spores, ABLC given at 12.8 mg/kg led to 10 of 10 animals that survived and 8 animals that were cleared of A. fumigatus. Three animals in the 0.8-mg/kg ABLC-treated group survived, with two being cleared of A. fumigatus, while no animals survived in the 0.8-mg/kg Fungizone group. All animals died in the fluconazole and itraconazole (100-mg/kg) groups. It should be noted that this is an acute infection model in which infection control animals died between 2 and 4 days. Therefore, static agents such as azoles would not be expected to be highly active under these conditions.

When therapeutic response was based on clearance, ABLC and Fungizone were both effective in eradicating the pathogen from lungs and kidneys. In the more severe infection induced by 10⁶ spores, ABLC maintained its effectiveness, while Fungizone, even at its maximum tolerated dose (0.8 mg/kg), failed to prolong the lives of the infected animals significantly. Fungizone was given intraperitoneally and ABLC was given intravenously to mice at doses of 0.2 to 12.8 mg/kg in a similar study in A. fumigatus-infected mice.
animals. There was no difference in the efficacies of ABLC and Fungizone; the clearance ED<sub>50</sub> were 7.5 and 7.8 mg/kg, respectively (data not shown). When Fungizone was given intraperitoneally at higher levels, there was no difference in the efficacies of ABLC and Fungizone in the Aspergillus model.

In another study in A. fumigatus-infected mice, a mixture of DMPG and DMPC (the lipids contained in ABLC) was administered intravenously at the same concentration of lipid present in the top dose of ABLC used (12.8 mg/kg/day). Administration of the lipids had no effect on the course of the infection, because the lipid-injected animals died at a rate parallel to that of the infection control mice.

**Cryptococcus infections.** The intravenous injection of 2 × 10<sup>5</sup> CFU of C. neoformans resulted in a disseminated infection, with 100% mortality occurring between 9 and 24 days. Organ distribution studies indicated that while all cultured organs had considerable numbers of cryptococci present, the brain was the most heavily infected. Therapy was initiated 2 days postinfection and was continued daily for 7 days. Surviving animals were sacrificed at 31 days, and brains and lungs from all surviving animals were cultured for the presence of cryptococci. Fungizone was the most effective preparation in terms of prolonging survival (Table 5), because no deaths occurred during the study in animals treated with 0.8 mg/kg. These surviving animals were heavily infected, however, with cryptococci recovered from the brains of 9 of 10 animals. ABLC was very efficacious in terms of survival, with an ED<sub>50</sub> of 1.8 mg/kg. Moreover, 6 of 10 animals were cleared of a brain infection at the top level of ABLC used (12.8 mg/kg).

In the group given fluconazole orally at 100 mg/kg/day for 5 days, only 2 of 10 animals survived, with brains and lungs of both surviving animals being heavily infected. No animals in the group given itraconazole at 100 mg/kg/day survived.

**Histoplasma infections.** Mice were injected intravenously with 5 × 10<sup>7</sup> yeast cells of H. capsulatum. All infection control animals died between 7 and 12 days with this inoculum. In animals with normal resistance mechanisms, all agents were effective based on 6-week survivals (Table 6), with the AmB preparations being more potent than the azoles. In animals immunosuppressed with triamcinolone, only ABLC and Fungizone retained their effectiveness (Fig. 2 and Table 6), with ED<sub>50</sub> of 0.7 and 0.3 mg/kg/day, respectively. Ketoconazole, itraconazole, and fluconazole at 100 mg/kg/day for 5 days failed to protect 50% of the treated mice.

### DISCUSSION

Liposomal formulations of AmB have been reported to be less toxic to humans and experimental animals than AmB given as Fungizone is. These preparations have been shown to be effective in the therapy of experimental fungal infections in animals as well as in the therapy of fungal infections in humans (26, 27). It has been difficult to evaluate and compare the safety and efficacy of liposomes from different laboratories because the methods of production, types of lipid, presence or absence of sterols, size, etc., are different. Lopez-Berestein and coworkers (12-16) have used DMPC, DMPG, and AmB in large multilamellar liposomes (over 1 μm in diameter). These AmB liposomes have been successful in the therapy of Candida, Aspergillus, Torulopsis, and Histoplasma infections in humans (12-14) as well as in the therapy of experimental Candida infections in mice (15, 16). A formulation composed of AmB, phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol was used by Katz et al. (9) to successfully treat a case of pulmonary aspergillosis in a heart transplant patient. This preparation consisted of liposomes of less than 0.1 μm in diameter. Gondal et al. (3) reported that a similar preparation was effective in the therapy of experimental systemic candidiasis in mice. Scullier et al. (21) used egg phosphatidylcholine, cholesterol, stearylamine, and AmB with a vesicle diameter of about 60 nm to treat Candida and Aspergillus infections in cancer patients. Some improvement was noticed in several patients after AmB liposomal therapy. Taylor et al. (23) and Graybill et al. (4) demonstrated that positively charged, multilamellar AmB liposomes were effective in treating experimental Histoplasma and cryptococcal infections in mice. The liposomes used in those studies contained ergosterol, sphingomyelin, and stearylamine. Tremblay and coworkers (24) used egg phosphatidylcholine, cholesterol, and tocopherol succinate to produce AmB-containing liposomes which were unilamellar with a diameter of 0.6 to 1 μm. This preparation was effective in treating a systemic Candida infection in mice.

In collaboration with The Liposome Co., we have developed a lipid complex with DMPC, DMPG, and AmB (8).
This stable complex can be produced consistently in large quantities. ABLC has the characteristics of an AmB liposome with reduced toxicity in experimental animals, efficacy against a variety of experimental fungal infections, and a propensity for uptake by reticuloendothelial systems.

It is interesting that there were some differences between ABLC and the preparation used by Gondal et al. (3), lip-AMB. Their preparation consisted of liposomes of less than 0.1 μm in diameter, compared with diameters of 1.6 to 11.1 μm for ABLC. There were differences in AmB levels in plasma, because lip-AMB produced levels in plasma markedly higher than those of Fungizone. In contrast, ABLC gave levels in plasma markedly lower than those of Fungizone. ABLC also was concentrated in the liver to a greater degree than lip-AMB was. However, both preparations were effective in treating experimental Candida infections in mice. ABLC was also effective in immunosuppressed animals infected with Candida as well as Aspergillus and Histoplasma isolates.

The reduced toxicity of AmB when administered as ABLC allows the therapeutic use of ABLC at levels of AmB previously considered to be toxic. The reason for this reduced toxicity has not been determined, but it may be related to a depot or sustained release of AmB from the lipid complex within the tissue, as has been suggested by Szoka et al. (22).

The relative failure of oral agents like itraconazole and fluconazole was somewhat surprising, because they have been reported to be effective in the therapy of experimental fungal infections in mice (5, 11, 25). In the current study, the model infections were designed to present a formidable challenge to the test agents, to reflect the severe problems that these systemic mycoses often present in seriously ill individuals. The failure of itraconazole against aspergillosis in immunosuppressed mice was likely due to the severity of the model, with infection control animals dying between 2 and 4 days. Itraconazole has been reported to be effective in a model of murine aspergillosis in which the animals were infected by the intravenous route (25). Itraconazole was given for 5 consecutive days beginning immediately before infection. In our study, treatment was delayed for 5 h and the infections were more severe.

The results obtained with Histoplasma infections in mice were of particular interest. In normal mice, all antifungal treatments were effective, including ketoconazole, itraconazole, and fluconazole. However, in animals immunosuppressed with triamcinolone, ABLC and Fungizone retained their efficacy while fluconazole, itraconazole, and ketoconazole showed a marked decrease in their therapeutic potentials.

Graybill et al. (5), in a study on the effectiveness of fluconazole against murine histoplasmosis, used an intranasal route for infection, with control animals dying between 20 and 30 days after infection. AmB and ABLC, in contrast, were effective for 40 days. It was demonstrated that AmB was effective in normal animals and was less toxic than ABLC. ABLC and Fungizone were effective in both groups of animals.

Kobayashi and coworkers (11), however, reported that *H. capsulatum*-infected AKR mice immunosuppressed with cyclophosphamide or cortisone could be effectively treated with fluconazole or AmB. In our study, immunosuppression with steroids markedly decreased the effectiveness of fluconazole. We did not decrease the infecting dose between normal and steroid-treated mice, as was done by Kobayashi et al. (11), which may have accounted for some of the differences noted between the two studies.

The increasing number of reports on the occurrence of fungal infections in individuals with depressed resistance mechanisms point out the need for new or improved antifungal agents. We evaluated the efficacy of ABLC against a variety of fungal infections in experimental animals. ABLC was effective against all model infections studied. Against some infections, ABLC and Fungizone had comparable efficacies, whereas Fungizone was more effective in other

### TABLE 6. Efficacy of ABLC against *H. capsulatum* infections in mice

<table>
<thead>
<tr>
<th>Prepn</th>
<th>ED₅₀ (mg/kg/day)</th>
<th>Normal mice</th>
<th>Immunosuppressed mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABLC</td>
<td>0.2 (0.15–0.25)</td>
<td>0.7 (0.5–0.9)</td>
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<tr>
<td>Fungizone</td>
<td>0.1 (0.04–0.16)</td>
<td>0.3 (0.2–0.4)</td>
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<tr>
<td>Fluconazole</td>
<td>2.8 (0.6–5.0)</td>
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</tr>
<tr>
<td>Itraconazole</td>
<td>10.5 (6–15)</td>
<td>&gt;100</td>
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</tr>
<tr>
<td>Ketoconazole</td>
<td>16.9 (11.3–22.5)</td>
<td>&gt;100</td>
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*a* *H. capsulatum* SC 15018 was used.

*b* The 95% confidence limits are given in parentheses.

![FIG. 2. Efficacy of ABLC against a systemic *H. capsulatum* infection in immunosuppressed mice. Animals were infected intravenously with 5 × 10⁶ yeast cells of *H. capsulatum* SC 15018 and were treated for 5 consecutive days beginning on day 3 of the infection. □, Infection control; ●, Fungizone, 0.8 mg/kg/day; ■, ABLC, 0.8 mg/kg/day; ▼, itraconazole, 100 mg/kg/day; △, ketoconazole, 100 mg/kg/day; ○, fluconazole, 100 mg/kg/day.](http://aac.asm.org/Downloaded from http://aac.asm.org/ on May 22, 2021 by guest)
studies. ABLC, with its increased therapeutic index, was successfully used to treat infections that could not be treated with Fungizone given at its maximum tolerated dose. ABLC may provide an invaluable adjunct to the therapy of serious fungal infections in humans, especially in immunodeficient individuals.

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