Comparison of Amphotericin B and N-D-Ornithyl Amphotericin B Methyl Ester in Experimental Cryptococcal Meningitis and Candida albicans Endocarditis with Pyelonephritis

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Amphotericin B and N-D-ornithyl amphotericin B methyl ester were compared for therapeutic efficacies against experimentally induced cryptococcal meningitis and Candida albicans endocarditis with pyelonephritis in rabbits. Antifungal activity of the two polyenes in vitro was similar for the yeasts used in these experiments. N-D-ornithyl amphotericin B methyl ester gave a slightly higher concentration in serum than amphotericin B did, but both drugs had similar elimination curves, and penetration into the cerebrospinal fluid was poor for both. Despite these similarities between the two polyenes, amphotericin B was much more effective than N-D-ornithyl amphotericin B methyl ester in the treatment of cryptococcal meningitis in rabbits. For C. albicans endocarditis, both polyenes had similar cure rates, but in vitro measurement of fungicidal activity in serum did not predict treatment outcome. For C. albicans pyelonephritis, both polyenes showed efficacy; because higher doses of the less toxic methyl ester could be used, it sterilized the urinary tract more often than amphotericin B. These studies indicate that in vivo and in vitro experiments may be needed to predict the results of treatment with polyenes.

The nephrotoxicity of amphotericin B can be mitigated by esterification of the parent molecule (13, 15). When a methyl group is esterified onto the carboxyl group of amphotericin B, antifungal activity is retained, but nephrotoxicity is reduced (15). Amphotericin B methyl ester has proved effective against candida, cryptococci, blastomyces, and coccidioides in animals (4, 7, 17) and has been used in humans (6, 11), but the drug was abandoned because it seemed to be neurotoxic (6).

Another polyene congener with less cardiac and renal toxicity than amphotericin B is N-D-ornithyl amphotericin B methyl ester (SCH 28191), which is soluble in water (15). This compound was selected by others from many polyenes for further evaluation because it retained antifungal activity similar to amphotericin B in vitro and its lower toxicity was appealing (15, 21). In this study we compared the therapeutic activities of N-D-amphotericin B methyl ester, the pharmacokinetics and in vivo activity of this polyene ester, and compared its activity with that of its parent amphotericin B against experimentally induced cryptococcal meningitis (23) and Candida albicans endocarditis (25) and pyelonephritis in rabbits. We attempted to correlate the results with the in vitro activities and the concentrations attained in the circulating blood and cerebrospinal fluid (CSF) of these animals.

MATERIALS AND METHODS

Animals. New Zealand White rabbits (2 to 3 kg) were housed in separate cages and given Rabbit Chow (Ralston Purina Co., St. Louis, Mo.) and water ad libitum. They were anesthetized with 100 to 150 mg of ketamine (Ketaset; Bristol Laboratories, Syracuse, N.Y.) plus 15 to 25 mg of xylazine (Rompun; Cutter Laboratories, Shawnee, Kan.) intramuscularly (i.m.) for all procedures.

Antifungal agents. Schering Corp. (Bloomfield, N.J.) kindly donated amphotericin B powder for in vitro studies; this was dissolved in dimethyl sulfoxide. For animal treatment studies the commercial preparation of amphotericin B, which contains Desoxycholate (E. R. Squibb & Sons Inc., Princeton, N.J.), was used. N-D-ornithyl amphotericin B methyl ester was provided by Schering; it was dissolved in sterile water for both in vitro and in vivo studies.

In vitro susceptibility testing. (i) To measure the MIC, an overnight growth of the yeast on a Sabouraud slant was taken up with a swab, suspended in saline, and adjusted by optical density to a final concentration of 10⁶ to 10⁷ CFU/ml in 1-ml tubes of Sabouraud broth. After the addition of antifungal agents, these tubes were incubated at 30°C for 24 h. The endpoint for growth inhibition was read as the first tube in the series which showed no visible growth. Subcultures of 0.1 ml onto Sabouraud agar were made for colony counts to quantitate the survivors; 99.9% kill of the original inoculum was defined as the minimal fungicidal concentration (26).

(ii) Blood for serum fungistatic and fungicidal titer was drawn after the first dose given to animals with endocarditis. Titer was measured with the test strain of C. albicans at an inoculum of 10⁵ CFU/ml. Dilutions of serum from treated rabbits were made in Sabouraud broth. Endpoints were read after 24 h, as above.

(iii) In vitro antifungal activity of the two polyenes in the presence of rabbit CSF was determined after adding 10⁶ CFU of Cryptococcus neoformans (DP strain) to normal rabbit CSF and then adding various concentrations of polyenes. Samples were removed at 2, 24, 48, and 72 h for subculture on Sabouraud agar to quantitate the number of viable yeasts.

Antimicrobial assays. Bioassay was performed on sera obtained from 2 to 6 randomly chosen rabbits infected with C. neoformans on day 1 of treatment. This assay was a modification of the method of Bennett et al. (1) with agar-well diffusion. The assay medium was antibiotic medium 12 (Difco Laboratories, Detroit, Mich.), with Saccharomyces
**TABLE 1. Serum and CSF concentrations of amphotericin B and N-\(\text{D-ornithyl amphotericin B methyl ester after i.v. injection of 1 or 5 mg/kg as measured by bioassay or HPLC}\)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Test agent(^a)</th>
<th>Dose (mg/kg)</th>
<th>Assay method</th>
<th>Serum Mean (\mu g/ml \pm SEM) (h after dose)</th>
<th>CSF Mean (\mu g/ml \pm SEM) (h after dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>1.0</td>
<td>4–6</td>
</tr>
<tr>
<td>AMB 1</td>
<td>Bioassay</td>
<td>1.1 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>AMB 1</td>
<td>HPLC</td>
<td>1.5 ± 0.2</td>
<td>1.1 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>0-AME</td>
<td>Bioassay</td>
<td>2.3 ± 0.6</td>
<td>2.0 ± 0.6</td>
<td>1.5 ± 0.4</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>0-AME</td>
<td>Bioassay</td>
<td>13.2 ± 2.0</td>
<td>9.2 ± 1.7</td>
<td>6.7 ± 0.3</td>
<td>3.9 ± 0.7</td>
</tr>
<tr>
<td>0-AME</td>
<td>HPLC</td>
<td>1.3 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
</tbody>
</table>

\(\text{a Two to six rabbits at each time period; bioassays and HPLC assays were done on different groups of rabbits.}
\(\text{b AMB, Amphotericin B; 0-AME, N-\(\text{D-ornithyl amphotericin B methyl ester.}
\(\text{c ND, Not done.}
\(\text{d Two rabbits had one measurement each of 0.029 and 0.027 \(\mu g/ml.}

*cerevisiae* as the test organism. Previous studies with this assay, which has a lower limit of sensitivity of approximately 0.3 \(\mu g/ml\), failed to detect amphotericin B in the CSF of treated animals (22).

A more sensitive high-pressure liquid chromatographic (HPLC) assay (14) was also performed on CSF and serum samples from infected animals on days 1 and 6 of treatment by Dr. Lin of Schering Corp. The assay for CSF samples had a lower limit of sensitivity for amphotericin B of 0.002 \(\mu g/ml\); the sensitivity for N-\(\text{D-ornithyl amphotericin B methyl ester was 0.008 \(\mu g/ml.\)}

For serum the lower limit of sensitivity for both polyenes was 0.015 \(\mu g/ml\).

**Organisms.** A human CSF isolate of *C. neoformans* (DP strain) used in previous experiments with cortisone-treated rabbits (23) was again used in the meningitis experiments. A clinical isolate of *C. albicans* (Carter strain) was used for the endocarditis and pyelonephritis experiments. These yeasts were maintained by serial transfer on Sabouraud slants.

**Production of cryptococcal meningitis.** Cultures (4 days old) of *C. neoformans* on Columbia blood agar plates containing 100 \(\mu g\) of chloramphenicol per ml were taken up on cotton swabs, suspended in 0.015 M phosphate-buffered saline, and adjusted to approximately 5 \(\times\) 10\(^7\) CFU/ml. Rabbits, treated i.m. with 2.5 mg of cortisone acetate (Merck Sharp & Dohme, West Point, Pa.) per kg of body weight 24 h before inoculation of yeast, were sedated, and 0.3 cc of the yeast suspension was inoculated intracerebrally. Rabbits were then treated daily with i.m. injections of 2.5 mg of cortisone acetate per kg for 18 days. At 4 days after inoculation, CSF was aspirated, and serial dilutions of CSF in phosphate-buffered saline were plated on Columbia blood agar plates containing chloramphenicol to prove that infection had been established. Rabbits were then randomly divided into treatment groups. Treatment was started on day 4 of infection, and CSF was withdrawn for yeast counts on days 7, 11, 14, and 18 of infection (that is, after days 3, 7, 10, and 14 of treatment). The duration of treatment was 2 weeks.

**Production of *C. albicans* endocarditis.** Rabbits were anesthetized, and the right carotid artery was exposed. A polyethylene catheter (PE-50; Clay-Adams, Parsippany, N.J.) was inserted across the aortic valve. The catheter was left in place until the rabbit was killed. At 24 h after catheter insertion, 1 ml of 1 \(\times\) 10\(^7\) CFU/ml of *C. albicans* was inoculated into the marginal ear vein. Rabbits were randomly divided into treatment groups 24 h later, receiving daily treatment for 7 days. After the last treatment (24 h), rabbits were killed, and the heart and kidneys were removed. Endocardial vegetations and sections of the renal cortex from the right kidney were removed, weighed, minced, and cultured quantitatively on Sabouraud agar plates. A sterile swab was touched onto the exposed renal pelvis and then streaked across a Sabouraud agar plate.

**Treatment regimens.** Rabbits were treated intravenously (i.v.) with either amphotericin B at a dose of 1 mg/kg per day or N-\(\text{D-ornithyl amphotericin B methyl ester at 1 or 5 mg/kg per day. Control rabbits receiving no treatment were included in each treatment experiment. Rabbits were allocated randomly to each group.**

**Statistical analysis.** In evaluating the effect of treatment on yeast counts, the slopes of curves for each rabbit with meningitis were compared with a t test for unpaired means. Fisher's exact test was used to compare the numbers with sterile CSF or tissue in each group.

**RESULTS**

The in vitro activity in Sabouraud broth of amphotericin B and N-\(\text{D-ornithyl amphotericin B methyl ester against the two yeast strains used was similar. The mean MICs of the two yeast species for amphotericin B and N-\(\text{D-ornithyl amphotericin B methyl ester follow: for amphotericin B, *C. neoformans* (0.03 \(\mu g/ml)\); for *C. albicans* (0.04 \(\mu g/ml)\); for N-\(\text{D-ornithyl amphotericin B methyl ester, *C. neoformans* (0.07 \(\mu g/ml)\); and *C. albicans* (0.08 \(\mu g/ml)\). The minimum fungicidal concentrations varied on repeated testing between 0.25 to 5.0 \(\mu g/ml\) for both yeasts but were consistently similar within each run. Moreover, the activity of the two polyenes against *C. neoformans* was indistinguishable when these drugs were added directly to CSF in vitro. The cryptococcal viability was not affected when incubation occurred in a subinhibitory dose (0.01 \(\mu g/ml\) of the two drugs in normal CSF. The rate of kill in vitro for both amphotericin B and N-\(\text{D-ornithyl amphotericin B methyl ester in CSF was identical at concentrations of 0.1 and 1.0 \(\mu g/ml\) (results not shown).**

Antifungal drug levels in serum of 2 to 6 randomly chosen rabbits infected with *C. neoformans* were measured by bioassay (Table 1). These levels were measured after a single i.v. dose. The concentration of N-\(\text{D-ornithyl amphotericin B methyl ester in serum was higher than that of amphotericin B at the same dose, but both drugs were measurable over the 24-h treatment period. Increasing the dose of N-\(\text{D-ornithyl amphotericin B methyl ester fivefold increased the measured serum concentration by a similar factor. No toxicity was observed when N-\(\text{D-ornithyl amphotericin B methyl ester was administered to rabbits i.v. at a dose of 5 mg/kg. In contrast, all of five rabbits receiving the same dose of**
amphotericin B died within 1 to 3 min after injection. At the end of 2 weeks of treatment with the two doses of N-D-ornithyl amphotericin B methyl ester and one dose of amphotericin B, no abnormalities were found in serum electrolytes or creatinine values for 4 to 5 animals in each group.

Drug concentrations measured by HPLC are also shown in Table 1. The sera and CSF measurements were done in rabbits infected with C. neoformans after the first dose. These samples were from different rabbits than those used to measure the drug by bioassay. Amphotericin B was detected in all CSF specimens but levels were very low, between 0.002 and 0.010 µg/ml. This is well below the amount that has any observable antifungal activity in vitro. After repeated dosing, accumulation did not occur; CSF levels remained constant after daily doses for 6 days (range, 0.006 to 0.008 µg/ml). N-D-ornithyl amphotericin B methyl ester was detected in the CSF of only two rabbits, at 0.029 and 0.027 µg/ml. However, the lower limit of susceptibility of this assay (0.008 µg/ml) was significantly higher than that for amphotericin B; it was also higher than most measured concentrations of amphotericin B in CSF (Table 1). Therefore, although we only occasionally measured levels of N-D-ornithyl amphotericin B methyl ester in the CSF, our data can neither support nor refute the likelihood that similar concentrations of both drugs entered the CSF during treatment. Neither agent achieved concentrations in the CSF which would be likely to have any direct antifungal activity as judged by their in vitro activity.

Despite the similar in vitro activity and serum pharmacokinetics of the two polyenes, the results of treatment of cryptococcal meningitis in rabbits were strikingly different. Amphotericin B at 1 mg/kg per day consistently sterilized counts in the CSF of rabbits over 2 weeks of treatment. Of 16 rabbits, 14 had no detectable yeast in the CSF. With similar doses of N-D-ornithyl amphotericin B methyl ester, this clearing of yeast was much less effective. Only two of eight surviving rabbits had undetectable counts of yeast in CSF (P < 0.01). Amphotericin B reduced CSF yeast counts faster than did N-D-ornithyl amphotericin B methyl ester at the 1 mg/kg per day dose (P < 0.01; Fig. 1). When the dose of N-D-ornithyl amphotericin B was increased to 5 mg/kg per day, the rate of killing of yeast in CSF increased somewhat, but it did not equal that of amphotericin B at the lower dose (Fig. 1). Thus, the activity of amphotericin B against C. neoformans was notably superior to that of N-D-ornithyl amphotericin B methyl ester.

In C. albicans endocarditis, the results of treatment were variable. Nearly half of the animals treated with either drug had sterile vegetations (Table 2). With N-D-ornithyl amphotericin B methyl ester treatment, rabbits were either cured of their infection or had yeast counts similar to controls, as if there had been no antimicrobial effect in some animals. This apparent all or none effect of N-D-ornithyl amphotericin B methyl ester is unexplained. Yeast cultured from the vegetations after 7 days of treatment remained fully susceptible to the polyenes used for treatment. On the other hand, amphotericin B usually exerted at least a suppressive effect. Both drugs cured nearly half of the animals (Table 2). N-D-ornithyl amphotericin B methyl ester at both doses produced higher serum fungistatic titers compared with amphotericin B. Only N-D-ornithyl amphotericin B methyl ester treatment produced any measurable fungicidal titers in serum (Table 3). However, there was no correlation between the serum titers and the outcome of treatment (P > 0.05). For example, one rabbit treated with N-D-ornithyl amphotericin B methyl ester which had the highest fungicidal titer (1:160) also had a heavy growth of yeast from vegetation at necropsy.

The effects of the polyenes on C. albicans infection of the kidney are shown in Table 2. Both amphotericin B and N-D-ornithyl amphotericin B methyl ester at equal doses

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**TABLE 2. Effects of amphotericin B and N-D-ornithyl amphotericin B methyl ester treatment on C. albicans endocarditis and pyelonephritis**

<table>
<thead>
<tr>
<th>Drug (mg/kg)</th>
<th>Dosage (mg/kg)</th>
<th>Endocarditis</th>
<th>Pyelonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SEM (log₁₀ CFU/g)</td>
<td>% Sterile</td>
</tr>
<tr>
<td>Control</td>
<td>None</td>
<td>6.8 ± 0.8</td>
<td>10</td>
</tr>
<tr>
<td>AMB</td>
<td>1</td>
<td>2.9 ± 0.6</td>
<td>35</td>
</tr>
<tr>
<td>0-AME</td>
<td>1</td>
<td>3.6 ± 0.9</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.6 ± 0.9</td>
<td>64</td>
</tr>
</tbody>
</table>

* For abbreviations, see Table 1, footnote b.

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**TABLE 3. Median serum fungistatic and fungicidal titers in rabbits with C. albicans endocarditis after the first dose of amphotericin B (1 mg/kg) or N-D-ornithyl amphotericin B methyl ester (1 or 5 mg/kg)*

<table>
<thead>
<tr>
<th>Drug (mg/kg/day)</th>
<th>Fungistatic titer</th>
<th>Fungicidal titer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predose*</td>
<td>Postdose*</td>
</tr>
<tr>
<td>AMB (1)</td>
<td>&lt;1:2</td>
<td>1:8</td>
</tr>
<tr>
<td>0-AME (1)</td>
<td>1:32</td>
<td>1:64</td>
</tr>
<tr>
<td>0-AME (5)</td>
<td>1:64</td>
<td>1:128</td>
</tr>
</tbody>
</table>

* Each group contained three to four rabbits.

* For abbreviations, see Table 1, footnote b.

* 24 h after previous dose.

* 1 h after dose.

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**FIG. 1.** Quantitative counts of C. neoformans in CSF of cortisone-treated rabbits (mean ± standard error [SE]). Rabbits received daily i.v. injections of 2 weeks metabolically active cortisone: amphotericin B (AMB), 1 mg/kg (24 rabbits); N.D-ornithyl amphotericin B methyl ester (AME), 1 mg/kg (18 rabbits) or 5 mg/kg (7 rabbits). No treatment was given to 14 control rabbits.
inhibited fungal growth in the majority of the kidneys from treated animals. When the daily dose of N-d-ornithyl amphotericin B methyl ester was increased to 5 mg/kg, more than 90% of the kidneys and their collecting systems were sterilized. Thus, as was observed in C. albicans endocarditis, the two drugs appeared to be similar in efficacy at the same doses. Unlike the results with endocarditis, for kidney infections there was evidence of increasing efficacy with increasing dosage.

DISCUSSION

Amphotericin B remains the standard against which all newer antifungal agents must be measured. N-d-ornithyl amphotericin B methyl ester is a water-soluble compound which was selected after a careful study of various amphotericin B congeners for in vitro activity against yeasts (12, 21); it also reduced acute toxicity on the cardiovascular system and long-term effects on the kidney (4). Previous studies with experimental animal infections of candidiasis (8), aspergillosis (9), histoplasmosis (16), and blastomycosis (19) showed that N-d-ornithyl amphotericin B methyl ester was active against these fungi in vivo.

We found little difference between the N-d-ornithyl amphotericin B methyl ester and its parent compound with respect to in vitro susceptibility of the two isolates of yeast used in these experiments. We were able to give significantly higher doses of the methyl ester congener compared with amphotericin B, because the former has less acute toxicity. Although no toxicity was evident in these short-term experiments, the possibility of neurotoxicity cannot be excluded.

The predictive value of fungal susceptibility testing has not been established. Stiller et al. (27) have suggested that in vitro susceptibility to flucytosine could be used to predict outcome of treatment in vivo in murine candidiasis, and Ryley et al. (24) have shown in vitro and in vivo correlation with several ketoconazole-resistant strains in murine infections. However, in a trial of ketoconazole in humans no relationship was found between in vitro testing of isolates and clinical response (5). For amphotericin B, it has been extremely difficult to correlate in vitro activity with in vivo response. Stimulation of cellular host defenses by amphotericin B, separate from its direct antifungal capacity, may play an important role in successful treatment (10). Our study emphasizes the importance of in vivo examination of these agents. Neither in vitro susceptibilities nor pharmacokinetics can explain why amphotericin B was distinctly more effective than N-d-ornithyl amphotericin B methyl ester in the treatment of cryptococcal meningitis in rabbits. Similar superiority of the parent compound over congeners in the treatment of experimental mycoses has been found by other investigators with another methyl ester compound (4, 5, 17).

Treatment of cryptococcal meningitis in rabbits parallels an important feature of treatment of fungal meningitis in humans. Amphotericin B is effective against these infections even though CSF concentrations are far too low to affect growth of C. neoformans in vitro (2). The poor penetration of N-d-ornithyl amphotericin B methyl ester into CSF is similar to that of amphotericin B and another methyl ester congener (18). The success of amphotericin B contrasts with experience in the treatment of bacterial meningitis, where drug concentrations in CSF can predict treatment outcome (28). It is possible that local concentrations of amphotericin B in the meninges themselves are higher than in CSF. Another possible explanation is that amphotericin B has immune modulatory activity on host cells which migrate toward the site of infection. If so, the results of our experiments suggest that the two polyenes have different potentials for interacting with host defenses. The effects of polyenes such as amphotericin B on host responses can be either stimulatory or inhibitory, depending on the systems examined (10). We found that the potency of various polyene preparations for macrophage activation in vitro varies. For example, amphotericin B is more effective than N-d-ornithyl amphotericin B and liposomal amphotericin B on a weight basis for activation of murine peritoneal macrophages to kill neoplastic cells (J. R. Perfect, D. L. Granger, and D. T. Durack, 24th Intern. Conf. Antimicrob. Agents Chemother., abstr. no. 570, 1984). Kobayashi et al. (16) found that the methyl ester congener is less active as an adjuvant for live mice in a murine B-cell activation assay than the parent compound amphotericin B. These results suggest that amphotericin B may be an active immune modulator, whereas esterification or other structural modifications may reduce this activity. Unfortunately, few in vivo data on the effect of amphotericin B on the host immune response during fungal infections are available (3). Further investigation into the interaction of amphotericin B and N-d-ornithyl amphotericin B methyl ester on host immunocytes, especially lymphocytes and macrophages during fungal infections, may help us understand the important interactions between these agents, the host, and the parasite.

C. albicans endocarditis is a serious infection which in the majority of cases requires valve replacement for cure (20). We attempted to increase polyene concentrations in serum during treatment of experimental endocarditis, hoping to improve killing of yeast in veins. N-d-ornithyl amphotericin B methyl ester, despite achieving higher levels in serum and consequently higher fungicidal activity in serum, could not improve on the mediocre antifungal effect of the parent compound (amphotericin B) in sterilizing infected vegetations. There was no correlation between the fungicidal and fungistatic titers and effects on counts of yeast in vegetations. In fact, N-d-ornithyl amphotericin B treatment either sterilized the vegetation or had no effect on candida growth in the vegetation; these disparate outcomes could not be correlated with serum concentrations of the drug. We conclude that the methyl ester congener, despite its water-soluble characteristics and higher serum concentrations, is no more effective in the treatment of C. albicans endocarditis than the parent compound. Polyene antimicrobial treatment in this model mirrors the experience in humans, which suggests a need for improved regimens. However, this lack of correlation between in vitro activity of these polyenes and in vivo results frustrates the clinical use of antifungals for endocarditis. New agents or combinations of agents should be critically analyzed in animal models before human use. Presently, valve replacement remains the cornerstone of therapy for fungal endocarditis (20).

Candida pylonephritis in the rabbit is a convenient and appropriate model in which to examine the effect of antifungal agents. Cultures can be obtained easily from kidney tissue, collecting system, and urine. With our candida strain, animals injected i.v. with yeasts survived 1 week without significant mortality; all kidneys were heavily infected. The higher dose (5 mg/kg per day) of N-d-ornithyl amphotericin B methyl ester was extremely effective in eradicating yeast from the urinary tract. In contrast to endocarditis, the effectiveness of polyene treatment of kidney infections with candida seems to be dose-dependent, with higher polyene serum concentrations eradicating yeast more rapidly from this site of infection.
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LITERATURE CITED


