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# NOTES

## Treatment of Experimental Disseminated Candidiasis with Cilofungin

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**The efficacy of cilofungin treatment of experimental disseminated candidiasis in rabbits was examined. Cilofungin treatment reduced yeast counts, especially in the kidney, with activity comparable to that of amphotericin B. The peak level of cilofungin in serum was measured at 5 min after administration of a single dose, with no drug detectable after 90 min.**

With the widespread use of potent antibacterial agents and the increasing number of immunocompromised patients, disseminated candidiasis has become a common medical problem. The primary antifungal agent used in the treatment of deep-seated *Candida* infections is amphotericin B. The well-described toxicities of this compound and its poorly defined dosage regimens have prompted the search for new potent antifungal drugs. The new azole compounds have shown promise in the treatment of disseminated *Candida* infections in animals but await definitive clinical trials in humans (4).

In the search for other new antifungal compounds, a unique analog of echinocandin B, cilofungin (LY121019), has been found to have potent in vitro activity against *Candida* species (1, 2, 5). This semisynthetic lipopeptide has been found to cause severe cell wall damage of *Candida* species by inhibition of β(1–3) glucan synthesis. (R. S. Gordee, D. J. Zeckner, and W. E. Alborn, Jr., Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother. abstr. no. 977, 1987). In previous investigations in this laboratory, the MICs of cilofungin were determined by broth dilutions in synthetic amino acid medium for fungi; the minimal fungicidal concentrations were determined to be the lowest drug concentration resulting in a 99% kill of the inoculum when plated onto Sabouraud agar (2). Cilofungin was shown to be particularly active against *Candida albicans* and *Candida tropicalis*, with fungicidal activity comparable to that of amphotericin B. For the *C. albicans* strain used in our in vivo model, the cilofungin MIC and MFC were 0.625 and 1.25 μg/ml, respectively.

Here, we examined the in vivo efficacy of cilofungin in rabbits with hematogenously disseminated *Candida* endocarditis, pyelonephritis, and endophthalmitis and compared its activity with that of amphotericin B. The right carotid artery of male New Zealand White rabbits (weight, 2 to 3 kg) was catheterized by standard procedures (3). Rabbits were then inoculated intravenously with $10^6$ blastospores of *C. albicans*. Twenty-four hours after inoculation, animals were randomized into the following groups: (i) untreated controls; (ii) cilofungin (Eli Lilly & Co., Indianapolis, Ind.) administered at 50 mg/kg twice a day intravenously for 7 days; and (iii) amphotericin B (E. R. Squibb & Sons, Princeton, N.J.) administered at 1 mg/kg per day intravenously for 7 days. Twenty-four hours after the last treatment, rabbits were sacrificed; and heart vegetations, kidneys, eyes, and urine were collected from each animal. Small tissue samples were selected, weighed, and homogenized; and quantitative cultures were performed on Sabouraud agar plates with chloramphenicol. Colony counts of tissue homogenates were expressed as the $\log_{10}$ CFU per gram of tissue. Urine and pelvic swabs were streaked onto plates, and growth was recorded as either positive or negative.

In the treatment of *Candida* endocarditis, cilofungin and amphotericin B reduced yeast counts by greater than 1 and 2.5 $\log_{10}$ CFU/g, respectively (Table 1). Only treatment with amphotericin B was found to significantly suppress infection compared with no treatment ($P < 0.05$ by the Tukey method for multiple comparisons). In the treatment of *Candida* endophthalmitis, the following resulted in significantly fewer positive cultures: amphotericin B treatment in the choroid and retina and either cilofungin or amphotericin B treatment in the vitreous body ($P < 0.05$ by the two-tail Fisher exact test). In rabbits with *Candida* pyelonephritis, both cilofungin and amphotericin B significantly reduced yeast counts in the renal cortex ($P < 0.05$ by the Tukey method for multiple comparisons). Cilofungin treatment virtually eliminated *Candida* species from the renal pelvis and urine.

Levels of cilofungin in serum were determined by an agar well diffusion protocol supplied by Eli Lilly & Co. by using *Aspergillus montevidensis* as the assay organism. A spore suspension (optical density at 590 nm, 0.60) from 3- to 4-day growth on V-8 juice agar was prepared and added to Biochem agar medium no. 3 (Biochem). Wells were cut in agar and filled with serum samples, and the zones of growth inhibition were measured. Drug concentrations in serum were calculated by using linear regression coefficients from the plot of standard zone sizes versus drug concentrations (1).

Cilofungin was rapidly excreted in rabbits (Fig. 1). Although a peak level of approximately 160 μg/ml was achieved in serum immediately following a single intravenous dose of 50 mg/kg, there was not detectable drug in the serum after 90 min (<0.3 μg/ml). After 7 days of therapy,

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TABLE 1. Effect of cilofungin and amphotericin B treatment on disseminated candidiasis

| Treatment | Pyelonephritis in renal cortex ($log_{10}$ CFU/g [no.])[a] | % Positive for pyelonephritis in: | | Endocarditis vegetations ($log_{10}$ CFU/g [no.])[a] | % Positive (no.) for endophthalmitis in: | |
|---|---|---|---|---|---|---|
| | | Renal pelvis | Urine | | Choroid and retina | Vitreous body |
| Cilofungin | 2.24 ± 0.62 (20) | 0 | 0 | 5.07 ± 1.00 (8) | 30 (10) | 30 |
| Amphotericin B | 1.67 ± 0.14 (22) | 13.6 | 0 | 3.75 ± 0.40 (18) | 9 (6) | 9 |
| None | 3.44 ± 0.22 (34) | 80 | 53.8 | 6.42 ± 0.60 (21) | 43 (17) | 70 |

[a] Values are the mean ± standard error of the mean.

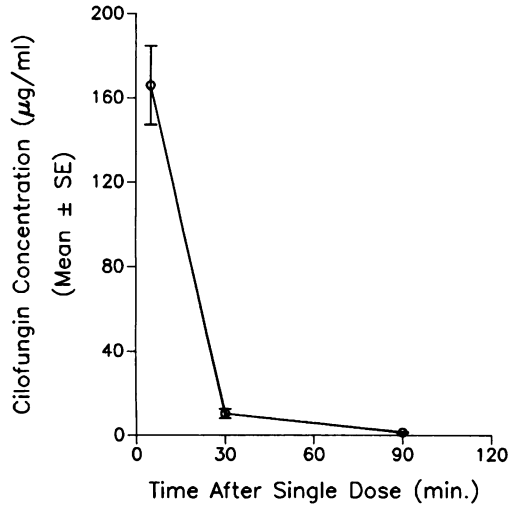


FIG. 1. Concentrations of cilofungin in serum after intravenous injection of 50 mg/kg in rabbits.

only two of four rabbits had detectable levels of cilofungin in urine (0.9 and 15.4 μg/ml).

In summary, the treatment of disseminated candidiasis with cilofungin resulted in yeast killing, despite the short half-life of the drug in rabbits. Infections in the urinary tract and eye were significantly reduced. Although in the heart, statistically significant effects could not be shown with the present regimen, there was a trend toward reducing yeast counts in cardiac vegetations. The rapid elimination of cilofungin in rabbits may have compromised its effectiveness. This may be species specific, since dogs showed a much slower rate of elimination of cilofungin (1). However, attention to the pharmacokinetics of cilofungin will be particularly important in future evaluations. A dosing regimen which can produce consistent and prolonged levels of cilofungin in serum is necessary; subsequent efficacy studies in the rabbit may require more frequent or continuous dosing. Further studies in other animal models are indicated.

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