ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1997, p. 1455–1459 Vol. 41, No. 7
0066-4804/97/$04.00+0

Efficacy of D0870 Treatment of Experimental *Candida* Vaginitis

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Received 20 February 1997/Returned for modification 2 April 1997/Accepted 20 April 1997

In this study, oral administration of the triazole D0870 was compared to oral administration of fluconazole in the treatment of experimental vaginal candidiasis. With an estrogen-dependent murine model of *Candida albicans* vaginal infection, the effects of D0870 on several isolates, including fluconazole-susceptible and -resistant isolates, were tested. D0870, at doses of 0.5 and 2.5 mg/kg of body weight given once over the course of a 10-day infection, was effective in eradicating vaginitis caused by fluconazole-susceptible laboratory and clinical isolates, respectively. In contrast, a stricter treatment regimen (every 24 to 48 h) with 10 and 25 mg of fluconazole per kg was required to achieve similar reductions in vaginal fungal titers induced by the same isolates. Whereas fluconazole was consistently ineffective in infections induced by fluconazole-resistant isolates, as predicted by in vitro susceptibility tests, D0870 was effective, although a daily regimen of 25 mg/kg was required. Additional studies showed that despite the in vitro activity of D0870 against two clinical *Candida glabrata* isolates, neither D0870 nor fluconazole was effective at daily doses as high as 100 and 125 mg/kg, respectively. Taken together, although D0870 failed to show efficacy against experimental *C. glabrata* vaginitis, D0870 was superior to fluconazole in the treatment of experimental *C. albicans* vaginitis caused by isolates that were either susceptible or resistant to fluconazole.

The increased prevalence of fungal infections in immunocompromised individuals, including AIDS (22, 24), transplantation (7), and cancer (20) patients, and the relative toxicity of amphotericin B have emphasized the urgency of developing more effective antifungal drugs. Azole derivatives, especially the triazole fluconazole, have proven to be highly effective in treating fungal infections (30). Unfortunately fungal infections resistant to fluconazole therapy have increased, especially in patients with AIDS and following transplantation (2, 29, 31, 32). Accordingly, prophylactic or prolonged fluconazole therapy in high-risk patients has been discouraged (3, 12) and development of new antimycotic agents has accelerated.

D0870 is a new triazole (Zeneca Pharmaceuticals, Macclesfield, Cheshire, United Kingdom) with a broad spectrum of activity and a significantly longer half-life than fluconazole (10, 11, 19). Compared to other azoles, D0870 has shown similar or increased activity in vitro against pathogenic fungal species, including those resistant to fluconazole (27, 39). D0870 has also shown significant in vivo activity against many fungal species, including efficacy in experimental infections caused by *Coccidioides immitis* (5), *Histoplasma capsulatum* (6), *Blastomyces dermatitidis* (4), *Cryptococcus neoformans* (8), and several *Candida* species (18, 21). In the majority of experimental models and in in vitro susceptibility tests, D0870 has been superior to fluconazole and most other azoles tested (4–6, 8, 18, 21).

With the exception of an intracerebral cryptococcal infection (8) and some preliminary data from Zeneca Pharmaceuticals from a murine vaginitis model (10), the efficacy of D0870 has against superficial or mucosal fungal infections not been evaluated. Vulvovaginal candidiasis (VVC) is a mucosal infection with significant infection rates in otherwise healthy women of child-bearing age (16, 17, 35). Greater than 85% of VVC cases are caused by *Candida albicans*, whereas *Candida glabrata* is recognized as the second most common *Candida* species and most common non-*C. albicans* species (16, 17, 26, 35, 37). To date, azoles, especially fluconazole, have been highly effective for treatment of attacks of VVC or recurrent VVC (33–36), and antifungal resistance has been rare (1, 23, 38). In contrast, *C. glabrata* vaginal infections have been more difficult to treat, and isolates are less susceptible in vitro to antimycotic agents (28, 35).

Our laboratory has employed an estrogen-dependent murine model of *C. albicans* vaginitis for several years. Infections are persistent for up to 8 to 10 weeks with high titers of organisms cultured from vaginal lavage fluid (13, 15). Recently, we also established a murine model of *C. glabrata* vaginal infection (14). The purpose of the present study was to compare the efficacies of D0870 and fluconazole for treatment of experimental *C. albicans* and *C. glabrata* vaginitis caused by both fluconazole-susceptible and -resistant isolates.

MATERIALS AND METHODS

Mice. Female CBA/J and nonobese diabetic (NOD/Lt) mice (Jackson Laboratories, Bar Harbor, Maine) were used throughout these studies. Mice were used at 7 to 8 weeks of age. The mice were housed according to specified guidelines at Wayne State University School of Medicine, an American Association of Laboratory Animal Care (AAALAC) accredited institution.

Drugs. D0870 (Zeneca Pharmaceuticals) was dissolved in sterile distilled water with 1% Tween 80. Fluconazole (Roehrig/Pfizer, New York, N.Y.) was dissolved in sterile distilled water. D0870 and fluconazole were filter sterilized, aliquoted, and stored at 4°C. Fresh aliquots of D0870, fluconazole, or the respective vehicles were administered orally to mice via a feeding needle in a volume of 0.2 ml.

Isolates. The laboratory *C. albicans* isolate employed was 3153A, which was used previously in our animal model of vaginitis (13). Three fluconazole-susceptible (identified by in vitro susceptibility and clinical outcome) *C. albicans* vaginal isolates (JH998.90, CD447.93, and DB597.94) were obtained from the bank of isolates collected at the Mott Center Vaginitis Clinic, Wayne State University School of Medicine. Three fluconazole-resistant (identified by in vitro susceptibility and clinical outcome) *C. albicans* oral isolates (DC, RC, and CPA-02) were obtained from a bank of AIDS clinical isolates at the Detroit Medical Center. Two *C. glabrata* vaginal isolates (LF574.92 and CS177.93) were obtained from the bank of specimens at the Mott Center Vaginitis Clinic. All isolates were previously identified to the species level by the appropriate morphological and

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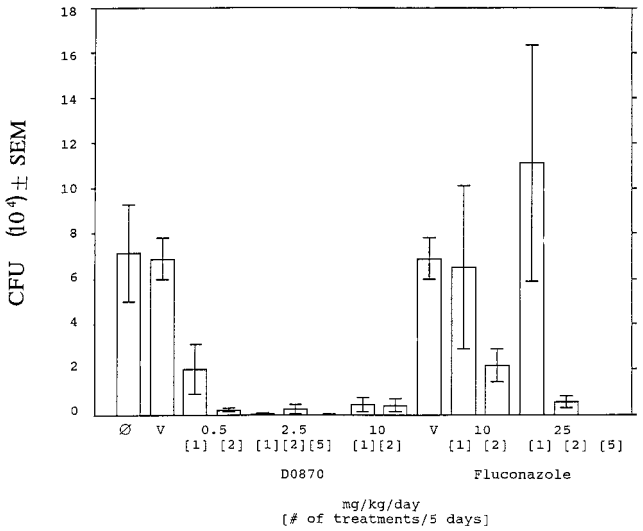

FIG. 1. Effects of D0870 on treatment of experimental vaginitis induced by *C. albicans*. Estrogen-treated groups of six CBA/J mice each were inoculated intravaginally with 5×10^5 *C. albicans* blastoconidia on day 0. Estrogen treatment was repeated on day 4. Oral treatments with D0870, fluconazole, or the respective vehicles (V) in a volume of 0.2 ml were given once (day 6), twice (days 6 and 8), or daily for five consecutive days (days 5 to 9). Vaginal fungal burden was assessed on day 10 by quantitative vaginal lavage culture. Results are expressed as CFU/100 μl of lavage fluid. The figure shows the dose of drug used and the number of treatments given over a 5-day period. A representative experiment of two repeats is shown.

biochemical tests and stored at −70°C in Phytone-peptone-glucose broth supplemented with litmus milk.

In vitro susceptibility testing. Antifungal susceptibility tests were performed according to National Committee for Clinical Laboratory Standards standard M27-T (25) with the microbroth assay (23). Fluconazole and D0870 were diluted serially (twofold) from 40 to 0.08 μg/ml in RPMI 1640 medium (GIBCO, Grand Island, N.Y.). Negative (without organism) and positive (without drug) growth controls were included for each isolate. Quality control isolates (*C. albicans* ATCC 90018 and *C. glabrata* ATCC 90030) were included for each respective experiment. Fresh colonies of each organism recovered from a Sabouraud-dextrose agar plate were suspended in sterile 0.85% saline and adjusted to the transmission of a 0.5 McFarland standard ± 1% at 530 nm. The suspension was diluted 1:2,000 in RPMI and added to drug-containing wells in a total volume of 200 μl. Plates were incubated at 35°C for 48 h. The MIC was defined as the first well with an approximate 80% reduction in growth compared to the growth of the positive control.

Experimental vaginitis. The estrogen-dependent murine models of *C. albicans* (CBA/J mice) and *C. glabrata* (NOD/Lt mice) vaginitis have been described previously (9, 14). Briefly, mice were treated with estradiol valerate (Sigma Chemical Co., St. Louis, Mo.) (4 mg/ml) subcutaneously in a volume of 0.1 ml 48 h prior to inoculation. Mice were inoculated with *C. albicans* (5×10^5) or *C. glabrata* (1×10^7) blastoconidia given intravaginally in a volume of 0.02 ml of phosphate-buffered saline. All organisms were prepared from a fresh stationary-phase culture grown overnight at 25°C. On day 4 after inoculation, estrogen was given again to all mice as described above. Daily oral treatment regimens of fluconazole and D0870 were begun on day 5 and continued through day 9 after inoculation. A two-dose treatment regimen of either drug was given on days 6 and 8 after inoculation. The one-dose treatment of D0870 was administered on day 6 after inoculation. Groups of six mice were used per drug or vehicle treatment. On day 10 after inoculation, all mice were sacrificed, and a vaginal lavage was performed with 100 μl of sterile phosphate-buffered saline. The lavage fluid was serially diluted and plated onto Sabouraud dextrose agar plates and incubated at 30°C for 48 h. CFU were determined and expressed as CFU/100 μl of lavage fluid.

RESULTS

Effects of D0870 on experimental *C. albicans* vaginitis. The effects of D0870 were compared to those of fluconazole for treatment of experimental vaginitis induced by a susceptible laboratory isolate of *C. albicans* (MICs: fluconazole, 0.16 μg/ml; D0870, 0.08 μg/ml). Mice were inoculated vaginally under conditions of pseudoestrus. The infection was evaluated 10 days after vaginal inoculation. D0870 was used in doses ranging from 0.5 to 10 mg/kg of body weight, while fluconazole was used in doses between 10 and 25 mg/kg of body weight. The drug treatments (oral) were given either once (day 6 after inoculation), twice (days 6 and 8 after inoculation), or for 5 consecutive days (days 5 to 9). The results in Fig. 1 show that compared to control mice treated with the vehicle, those treated one to five times with 0.5, 2.5, or 10 mg of D0870 per kg had significantly reduced vaginal titers of *C. albicans* ($P <$ 0.004 to 0.006). Clearance of infection (defined as sterile lavage fluid) was observed when 2.5 mg of D0870 per kg was given for 5 consecutive days (days 5 to 9) ($P < 0.0002$). In fluconazole-treated mice, at least two treatments with 10 mg/kg were required to reduce vaginal fungal burden compared to vehicle-treated control mice ($P < 0.008$). Clearance of detectable yeast was observed following five consecutive daily treatments with 25 mg/kg ($P < 0.003$). In all experiments, *C. albicans* vaginal population numbers in vehicle-treated infected mice were similar to that in untreated infected mice.

Effects of D0870 on *C. albicans* vaginitis induced by fluconazole-susceptible and -resistant clinical isolates. To examine the effects of D0870 on the treatment of infection caused by fluconazole-susceptible and -resistant isolates, clinical isolates were chosen on the basis of in vitro susceptibilities and used separately to induce vaginitis in the animal model. The MICs of fluconazole and D0870 for each respective isolate are shown in Table 1. The fluconazole-susceptible isolates as well as the laboratory strain were equally susceptible to both fluconazole and D0870. In contrast, the MICs of D0870 for the three fluconazole-resistant isolates were significantly higher (0.31 to 0.62 μg/ml), but did not approach those of fluconazole (>40 μg/ml).

Figure 2 shows the results of D0870 and fluconazole for treatment of vaginal infection caused by one of the fluconazole-susceptible isolates (CD447.93). Doses and treatment regimens for each drug were based on results obtained with the laboratory strain (Fig. 1). D0870 was used at doses of 2.5 to 25 mg/kg given one to five times, while fluconazole was used at 25 to 50 mg/kg given two to five times. Compared to mice treated

TABLE 1. In vitro susceptibility of *C. albicans* and *C. glabrata* isolates to fluconazole and D0870

Isolate	MIC (μg/ml)[a]	
	Fluconazole	D0870
Candida albicans		
Laboratory isolate	0.16	0.08
Fluconazole susceptible[b]		
JH998.90	0.16	0.08
CD447.93	0.16	0.08
DB597.94	0.16	0.08
Fluconazole resistant[b]		
DC	>40	0.31
RC	>40	0.62
CPA-02	40	0.31
Candida glabrata		
ATCC 90030	10	0.31
LF574.92	20	1.25
CS177.93	10	0.63

[a] Defined as the first concentration with which the isolate showed an approximate 80% reduction in growth compared to that in wells without drug (positive control).

[b] Determined by prior in vitro susceptibility tests with fluconazole and clinical outcome.

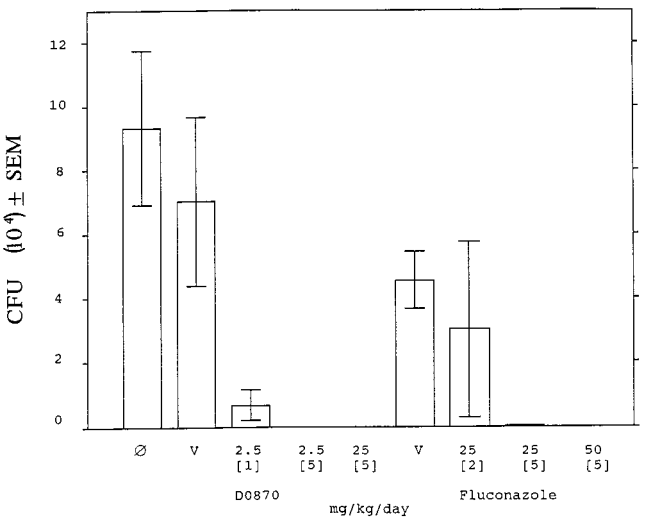

FIG. 2. Effects of D0870 on treatment of experimental vaginitis induced by a fluconazole-sensitive *C. albicans* clinical isolate (CD447.93). Estrogen-treated groups of six CBA/J mice each were inoculated intravaginally with 5×10^5 *C. albicans* blastoconidia on day 0. Estrogen treatment was repeated on day 4. Oral treatments with D0870, fluconazole, or the respective vehicles (V) in a volume of 0.2 ml were given once (day 6), twice (days 6 and 8), or daily for five consecutive days (days 5 to 9). Vaginal fungal burden was assessed on day 10 by quantitative vaginal lavage culture. Results are expressed as CFU/100 μl of lavage fluid. The figure shows the drug doses used and the number of treatments given over a 5-day period. A representative experiment of two repeats is shown.

with the vehicle, mice treated once (day 6 after inoculation) with D0870 at 2.5 mg/kg had reduced vaginal fungal burden ($P < 0.026$). Eradication of infection was observed with either 2.5 or 25 mg/kg/day for 5 consecutive days ($P < 0.0002$). In fluconazole-treated mice, while 25 mg/kg given twice (days 6 and 8) had no effect on vaginal fungal burden compared to that in vehicle-treated mice, five consecutive treatments (days 5 to 9) with 25 mg/kg showed reduced fungal titers ($P < 0.002$). Clearance of infection was observed following five daily treatments of 50 mg/kg/day ($P < 0.002$). Results were similar for the other two fluconazole-susceptible *C. albicans* isolates (JH998.90 and DB597.94) (data not shown).

The effects of D0870 on treatment of vaginitis caused by a fluconazole-resistant isolate (RC) are illustrated in Fig. 3. Compared to control mice treated with vehicle, mice treated orally for 5 consecutive days (days 5 to 9) with D0870 at 25 and 100, but not 2.5, mg/kg/day showed reduced vaginal fungal titers ($P < 0.008$ and 0.014, respectively). In contrast, mice treated for 5 consecutive days (days 5 to 9) with fluconazole at either 25, 50, or 125 mg/kg/day had no effect on vaginal fungal burden. Identical results were obtained with two other fluconazole-resistant *C. albicans* isolates (DC and CPA-02) (data not shown).

Effects of D0870 on vaginitis induced by *C. glabrata*. A recently developed murine model of *C. glabrata* vaginitis in NOD mice (14) was employed to evaluate the in vivo efficacy of D0870 against two clinical *C. glabrata* isolates (LF574.92 and CS177.93) considered susceptible to D0870 as per in vitro susceptibility tests. The MICs of D0870 were considerably lower than that of fluconazole for both *C. glabrata* clinical isolates and a quality control American Type Culture Collection *C. glabrata* isolate (Table 1). However, neither the mice treated for 5 consecutive days with D0870 at doses of up to 100 mg/kg/day or those treated with fluconazole at doses of up to 125 mg/kg/day showed any reduction in vaginal *C. glabrata* titers caused by either isolate (data not shown).

To confirm that the lack of effects of D0870 against *C. glabrata* was the result of the organism and not the strain of mice, the NOD mice were infected with *C. albicans* (laboratory strain) and treated for 5 consecutive days with D0870 (2.5 mg/kg) or fluconazole (50 mg/kg). Compared to the vehicle-treated control mice, mice treated with either D0870 or fluconazole had significantly lower vaginal *C. albicans* titers ($1.5 \times 10^6 \pm 8 \times 10^5$ CFU versus $2.3 \times 10^4 \pm 8.2 \times 10^3$ CFU, $P < 0.04$; and $3.1 \times 10^5 \pm 2.2 \times 10^5$ CFU versus $1.4 \times 10^4 \pm 1.3 \times 10^4$ CFU, $P < 0.03$, respectively).

DISCUSSION

This study demonstrates that the triazole D0870 was superior to fluconazole in the treatment of experimental vaginitis caused by fluconazole-susceptible and -resistant isolates of *C. albicans*. For infections caused by the fluconazole-susceptible laboratory isolate, D0870 given in a single dose as low as 0.5 mg/kg showed significant reductions in vaginal fungal burden. For infections caused by fluconazole-susceptible clinical isolates, doses of D0870 as low as 2.5 mg/kg were efficacious, with eradication of infection observed with a daily treatment regimen. In contrast, treatment of infections induced by the same isolates with fluconazole required multiple doses between 10 and 25 mg/kg. Taken together, D0870 was at least 10-fold more active than fluconazole, with fewer doses required for successful treatment.

The efficacious doses and treatment regimens of D0870 and fluconazole for *C. albicans* vaginitis were consistent with the murine pharmacokinetics for each drug. Satisfactory results observed following a single dose of D0870 given on day 6 of the 10-day infection are consistent with the drug's relatively long half-life of 36 h (10, 11). The short 4.5-h half-life of fluconazole (19) supports the requirement for multiple doses of fluconazole and is a probable explanation for why positive results

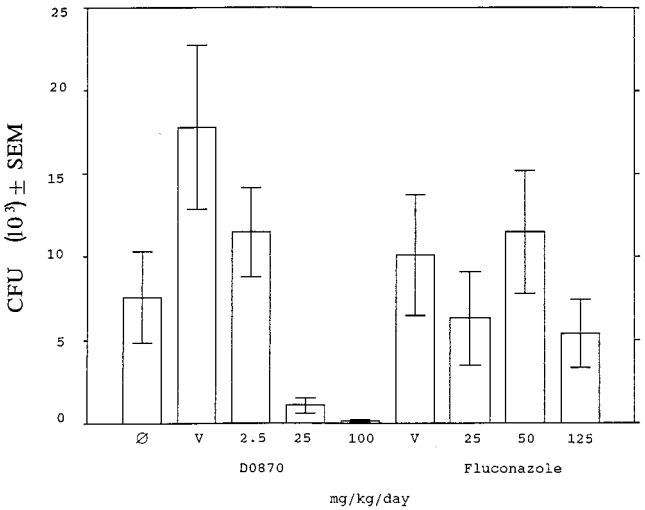

FIG. 3. Effects of D0870 on treatment of experimental vaginitis induced by a fluconazole-resistant *C. albicans* clinical isolate (RC). Estrogen-treated groups of six CBA/J mice each were inoculated intravaginally with 5×10^5 *C. albicans* blastoconidia on day 0. Estrogen treatments were repeated on day 4. Oral treatments with D0870, fluconazole, or the respective vehicles (V) in a volume of 0.2 ml were given for 5 consecutive days beginning on day 5. Vaginal fungal burden was assessed on day 10 by quantitative vaginal lavage culture. Results are expressed as CFU/100 μl of lavage fluid. The figure shows the dose employed for each group. A representative experiment of two repeats is shown.

with two doses of 10 mg of fluconazole per kg given on days 6 and 8 could not be duplicated with 1 dose of 25 mg/kg given on day 6 alone.

Of particular significance was the effectiveness of D0870 against infections caused by several fluconazole-resistant *C. albicans* isolates. In fact, the requirement for higher daily doses of D0870 to achieve the same level of efficacy observed against infections caused by fluconazole-susceptible isolates was predicted based on in vitro susceptibility results, which were 2 to 3 dilutions higher for the fluconazole-resistant isolates than those for the laboratory or fluconazole-susceptible isolates. Thus, the efficacy of D0870 for treatment of experimental vaginal *C. albicans* infections appears to correlate with in vitro activity.

In contrast to the efficacy of D0870 and fluconazole against *C. albicans* vaginitis, neither D0870 nor fluconazole could reduce vaginal fungal burden caused by two clinical *C. glabrata* isolates. While the failure with fluconazole may have been predicted by the relatively high MIC for each isolate (10 and 20 μg/ml), the MICs of D0870 (0.63 to 1.25 μg/ml) might have predicted some level of in vivo efficacy. However, five consecutive daily doses of D0870 as high as 100 mg/kg (representing 40- and 4-fold-higher doses than were effective against infections caused by fluconazole-susceptible and -resistant isolates, respectively) had no effect on the experimental *C. glabrata* vaginal infection. Although these isolates were chosen based on the relatively low MICs of D0870 for them, it is unknown whether higher concentrations of D0870 would be effective or whether efficacy could be achieved against isolates that are more susceptible to D0870. Nevertheless, to exclude the possibility that D0870 was ineffective because of the strain of mice employed, D0870 and fluconazole were evaluated for treatment of *C. albicans* vaginal infection in NOD mice. Efficacy with both D0870 and fluconazole confirmed that the ineffectiveness of the drugs against the *C. glabrata* infection was indeed related to the organism and not the strain of mouse. Thus, our results suggest that both triazoles are ineffective against experimental *C. glabrata* vaginal infections and that unlike *C. albicans* infections, in vitro susceptibility tests with D0870 do not appear predictive of in vivo activity.

The efficacy of D0870 and its superiority compared to fluconazole in the murine model of *C. albicans* vaginitis are consistent with the effects of D0870 in other murine models of *Candida* infections, as well as those of other medically important fungi (4–6, 18, 21). In each, D0870 was found to be effective at low doses and was superior to fluconazole. This is, however, the first report describing the efficacy and superiority of D0870 against mucosal *Candida* infections.

In summary, although D0870 was ineffective against experimental vaginal *C. glabrata* infections, D0870 was highly effective and superior to fluconazole for treatment of experimental vaginal *C. albicans* infections caused by fluconazole-susceptible isolates (laboratory and clinical), as well as all fluconazole-resistant isolates tested. The pharmacokinetic advantages and superior activity of D0870 against *C. albicans* indicate a potentially useful clinical role for D0870 in the treatment of systemic as well as mucosal *Candida* infections.

ACKNOWLEDGMENT

This work was supported by Zeneca Pharmaceuticals.

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