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Fluconazole, D0870, and Flucytosine Treatment of Disseminated *Candida tropicalis* Infections in Mice

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D0870 is a recently developed triazole with characteristics of a broad spectrum of activity and slow clearance by nonrenal mechanisms. Herein we have evaluated the efficacy of D0870, alone and combined with flucytosine, in a murine model of disseminated *Candida tropicalis* infection. Four isolates of *C. tropicalis* were evaluated. Two were highly susceptible in vitro to fluconazole, and two were resistant to fluconazole. All were highly susceptible to flucytosine and D0870. Animals were pretreated with 5-fluorouracil 1 day before infection because *C. tropicalis* has reduced virulence in immunocompetent mice. This was done to render them neutropenic for >10 days. Mice were infected intravenously and treated orally with D0870 or fluconazole, alone or combined with flucytosine. Survival and tissue burden of the spleen and kidneys were used to evaluate the efficacy of antifungal therapy. Fluconazole was less effective for treatment of resistant *C. tropicalis* than susceptible *C. tropicalis*. D0870 was more potent than fluconazole and was effective in fluconazole-resistant isolates. Flucytosine was consistently effective when used alone but did not consistently add to the benefit of D0870 or fluconazole. D0870 has potential in treatment of candidiasis caused by *C. tropicalis*, including fluconazole-resistant isolates.

D0870 is a new antifungal triazole with significant activity against *Candida albicans*, including fluconazole-resistant isolates (5, 6). While fluconazole resistance has been slowly increasing in *C. albicans*, it has been more consistently present in non-*albicans Candida* species. One of these species is *Torulopsis glabrata*, which is also commonly resistant to fluconazole and may respond to treatment with D0870 (2). Another non-*albicans* species of considerable clinical importance is *Candida tropicalis*. *C. tropicalis* is much less commonly isolated from clinical specimens than *C. albicans* but when present is usually associated with disease rather than colonization as a commensal (like *C. albicans*) (10).

In more serious *Candida* infections, amphotericin B is sometimes combined with flucytosine for synergistic activity (4). However, in murine cryptococcal infections, it has recently been acknowledged that fluconazole and flucytosine interact beneficially (1). In the present study, we have compared the efficacies of fluconazole, D0870, and flucytosine in treatment of murine disseminated candidiasis. We also evaluated whether there is any benefit of adding flucytosine to triazoles in treatment of this infection.

MATERIALS AND METHODS

Four clinical isolates of *C. tropicalis* were selected. Susceptibility testing was accomplished by a macrobroth dilution utilizing the National Committee for Clinical Laboratory Standards proposed standard for antifungal susceptibility testing of yeasts (M27-P) (9). Inocula were standardized by spectrophotometer to a 0.5 McFarland standard, diluted 1:100 in sterile distilled water, and finally diluted 1:20 into RPMI 1640 (American Biorganics, Niagara Falls, N.Y.). After incubation at 35°C, MICs were determined at 24 and 48 h as the lowest drug concentration with at least 80% reduction in turbidity compared with the drug-free control tube. Drug combinations were tested by adapting the procedure mentioned above to a checkerboard macrobroth dilution technique. The MICs are indicated in Table 1. Isolates 510 and 681 were considered susceptible to fluconazole, D0870, and flucytosine, while isolates 231 and 168 were resistant to fluconazole but susceptible to the other two drugs.

C. tropicalis was maintained on Sabouraud dextrose agar and 1 day before infection was inoculated into brain heart infusion broth and incubated for 24 h at 37°C. Organisms were washed in normal saline, diluted, and counted in a hemacytometer. There was no aggregation of cells. The cells were diluted to the desired inoculum: between 3×10^5 and 2×10^8 CFU per mouse. This was confirmed by quantitative cultures. ICR outbred mice were housed in groups of five and had access to food and water ad libitum. One day before infection, mice were given 5-fluorouracil at 150 mg/kg of body weight, a dose which reduced the peripheral blood neutrophil count to $<100/\mu l$ for >10 days. Mice were infected intravenously with *C. tropicalis* in a 0.2-ml volume.

Treatment began 1 day after infection. Controls were not treated. Mice treated with flucytosine initially were given one-third of the total daily dose every 8 h orally by gavage. Because this method was tedious and possibly more traumatic to mice, we independently determined that infected mice drink about 4 ml per mouse per day through most of the course of mycotic disease. We then provided the daily dose in drinking water, with each mouse estimated to consume 4 ml/day. In addition to being less traumatic, we believe that this improved efficacy because bolus doses of flucytosine are very rapidly cleared by mice. D0870 (dissolved in 0.05% Tween 80) was given either daily or every other day. Fluconazole (dissolved in 0.3% Noble agar) was given twice daily because it is cleared by mice much more rapidly than D0870 (7). For survival studies, mice were treated from day 1 through day 10. In some studies, mice were then observed for survival through day 30, and in others, they were observed through day 46. Moribund mice were sacrificed, and their deaths were recorded as occurring on the next day. For tissue burden studies, mice were treated from day 1 through day 5 and sacrificed 1 day later for quantitative tissue cultures of the spleen and both kidneys.

For survival studies, groups of 10 mice were used, and for quantitative cultures, groups of 7 mice were used. For determination of significance, the log rank and Wilcoxon tests were used for survival and Tukey's studentized range test was used for comparisons of tissue counts. Because of multiple comparisons in the same analysis, the P value for significance was <0.01.

TABLE 1. MICs of fluconazole, D0870, and flucytosine at 24 h

Isolate	MIC (μg/ml) at 24 h		
	Fluconazole	D0870	Flucytosine
510	2.5	≤0.125	≤0.125
681	≤1.25	≤0.125	0.25
231	>80	0.25	≤0.125
168	20	≤0.125	≤0.125

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TABLE 2. Survival of mice infected with fluconazole-susceptible *C. tropicalis* and treated with fluconazole, flucytosine, or D0870

Isolate	Drug[a]	Dosage (mg/kg/day)[b]	Mean survival (days) ± SE	% Mortality at day 30
510				
Study 1	None		5 ± 0.4	100
	Flucytosine	20 in H_2O	11 ± 1.2[c]	100
	Fluconazole	0.1 BID	8 ± 2.6	90
	Fluconazole + flucytosine	0.1 BID + 20 in H_2O	13 ± 3.0	90
	D0870	0.2	5 ± 0.3	100
	D0870 + flucytosine	0.2 + 20 in H_2O	11 ± 3.1	90
Study 2	None		11 ± 1.5	100
	Flucytosine	120 in H_2O	16 ± 3.9	70
	Fluconazole	0.5 BID	8 ± 1.0	100
	Fluconazole + flucytosine	0.5 BID + 120 in H_2O	20 ± 4.0	60
	D0870	1.0	23 ± 3.2[c]	50
	D0870 + flucytosine	1.0 + 120 in H_2O	17 ± 5.0	70
Study 3	None		12 ± 3.9	90
	Flucytosine	240 in H_2O	39 ± 4.9[c]	20
	Fluconazole	2.5 BID	24 ± 5.0[c]	70
	Fluconazole + flucytosine	2.5 BID + 240 in H_2O	30 ± 5.3	60
	D0870	10 on alternate days	44 ± 2.4[c]	10
	D0870 + flucytosine	10 on alternate days + 240 in H_2O	32 ± 4.9[c]	60
Study 4	None		23 ± 6.3	60
	Flucytosine	80 TID	35 ± 4.7	40
	Fluconazole	15 BID	46 ± 0[c]	0
	Fluconazole + flucytosine	15 BID + 80 TID	37 ± 4.9	30
	D0870	30	46 ± 0[c]	0
	D0870 + flucytosine	30 + 80 TID	42 ± 3.7[c]	10
681				
Study 1	None		6 ± 0.5	100
	Flucytosine	60 in H_2O	19 ± 2.2[c]	80
	Fluconazole	0.5 BID	12 ± 1.6[c]	100
	Fluconazole + flucytosine	60 in H_2O + 0.5 BID	25 ± 2.3[c]	50
	D0870	0.2	6 ± 0.3	100
	D0870 + flucytosine	0.2 + 60 in H_2O	17 ± 2.9[c]	80
Study 2	None		18 ± 3.9	60
	Flucytosine	120 in H_2O	31 ± 1.3[c]	10
	Fluconazole	0.5 BID	22 ± 3.5	50
	Fluconazole + flucytosine	0.5 BID + 120 in H_2O	27 ± 3.0	30
	D0870	1.0	27 ± 3.2	30
	D0870 + flucytosine	1.0 + 120 in H_2O	32 ± 0.1[c]	0
Study 3	None		7 ± 0.3	100
	Flucytosine	240 in H_2O	19 ± 1.6[c]	70
	Fluconazole	2.5 BID	10 ± 1.0[c]	100
	Fluconazole + flucytosine	2.5 BID + 240 in H_2O	21 ± 1.6[c]	60
	D0870	10 on alternate days	34 ± 14[c]	30
	D0870 + flucytosine	10 on alternate days + 240 in H_2O	26 ± 0[c]	10
Study 4	None		13 ± 3.8	90
	Flucytosine	80 TID	32 ± 5.8[c]	40
	Fluconazole	15 BID	38 ± 4.3[c]	30
	Fluconazole + flucytosine	15 BID + 80 TID	31 ± 5.4[c]	50
	D0870	30	46 ± 0[c]	0
	D0870 + flucytosine	30 + 80 TID	34 ± 6.0[c]	30

[a] Note that no combination was better than either drug individually.
[b] Abbreviations: BID, twice a day; TID, three times a day.
[c] Treatment superior to control.

RESULTS

Each organism was evaluated for synergy, additivism, or indifference at 48 h. The drug combination was deemed synergistic if the MIC was reduced two tubes, or fourfold, for both drugs. If the MIC resulted in only a one-tube, or twofold, reduction, then the combination was considered to be additive. Indifference was noted when the drug combinations failed to lower individual drug MICs. By these criteria, flucytosine, when tested in combination with fluconazole, appeared additive in all four isolates. However, when flucytosine was combined with D0870, additivism was noted only in two of the isolates (168 and 510), while the other two appeared indifferent.

TABLE 3. Tissue counts of *C. tropicalis* isolate 681

Drug	Dosage (mg/kg/day)	Tissue counts of isolate 681 (CFU/g [10^5])		
		Median	Range	
			Lower	Upper
Spleen				
None		14	5.0	90
Flucytosine	60 in H_2O	0.15[a]	0.09	22
Fluconazole	0.5 BID[b]	1.2[a]	0.14	2.8
Fluconazole + flucytosine	0.5 BID + 60 in H_2O	0.04[c]	0.002	0.08
D0870	0.2	7.5	0.63	3,730
D0870 + flucytosine	0.2 + 60 in H_2O	0.09[a]	0.007	0.6
Kidney				
None		31,900	5,160	166,000
Flucytosine	60 in H_2O	531[a]	90	39,900
Fluconazole	0.5 BID	3,600	2,450	18,500
Fluconazole + flucytosine	0.5 BID + 60 in H_2O	326[a]	17	2,570
D0870	0.2	23,200	4,890	110,000
D0870 + flucytosine	0.2 + 60 in H_2O	540[a]	54	21,200

[a] Treatment reduced the count significantly below that of control.
[b] BID, twice a day.
[c] Combination reduced the count significantly below that of either drug individually.

For *C. albicans*, fluconazole resistance in vitro has appeared to correlate best with failure to respond to 0.5-mg/kg or lower daily doses of fluconazole, whereas this dose was effective in animals infected with in vitro-susceptible isolates (8). Because such studies have not been conducted broadly for infection with *C. tropicalis*, we explored a broad range of treatment doses with all agents.

Survival data for fluconazole-susceptible isolates 510 and 681 are presented in Table 2. For isolate 510, flucytosine dosages as low as 20 mg/kg/day in water significantly prolonged survival of mice. At increasing doses of flucytosine, the response was not linear, and it is unclear why 120 mg/kg/day did not significantly prolong survival over that of controls. Fluconazole was not protective at a dosage of less than 2.5 mg/kg twice daily, while D0870 was protective at 1.0 mg/kg/day or more.

For isolate 681, flucytosine at dosages of 60, 120, and 240 mg/kg/day in water was protective, as was 80 mg/kg given every 8 h. Fluconazole at 2.5 and 15 mg/kg twice daily was protective and at 0.5 mg/kg twice daily was significantly protective in study 1 but not in study 2. D0870 was protective at a high dosage of 30 mg/kg/day and at 10 mg/kg/day on alternating days but not at 0.2 or 1.0 mg/kg/day. Again, flucytosine did not extend survival beyond that of either flucytosine or the triazole alone.

Tissue counts (Table 3) provide an additional perspective of the effect of therapy on isolate 681. In general, kidney counts were much higher than spleen counts. Flucytosine, at 60 mg/kg/day in water, reduced median tissue counts in both organs on the order of 2 logs, highly significant differences. Fluconazole at a low dose gave 1-log reductions in spleen and kidney tissue counts, but these were significant only in the spleen. The combination of triazole and flucytosine was superior to both drugs in the spleen, providing a further log reduction in tissue counts but not in the kidneys, in which counts were very similar to those with flucytosine alone. D0870 was ineffective when given alone in the low doses used, although there was an additive effect with flucytosine.

Two fluconazole-resistant isolates, 168 and 231, were also examined (Table 4). For isolate 168, at a total dosage of 0.2 mg/kg/day (study 1), neither fluconazole nor D0870 showed any benefit, and the low 20-mg/kg/day dosage of flucytosine did not show benefit alone or combined with the triazoles. Slightly higher doses of fluconazole and D0870 were protective (Table 4, study 2), but when the flucytosine dosage was raised to ≥40 mg/kg/day in drinking water or to 80 mg/kg every 8 h, there was significant protection. The combination of flucytosine and fluconazole was superior to both drugs given alone in study 4, but over the broad range of dosing, this was not shown again in any other combinations.

The final isolate examined, 231, was also fluconazole resistant in vitro. Flucytosine was protective at ≥60 mg/kg/day in drinking water or given at 80 mg/kg every 8 h (Table 4). Fluconazole showed no protection at any of the doses. D0870 was beneficial at ≥1.0 mg/kg/day and was superior to fluconazole at 0.5 mg/kg twice daily. Again, combined triazole and flucytosine did not confer any additional benefit over that for either drug alone.

Fungal tissue counts supported the survival data at one dosing level (Table 5). At a dosage of 60 mg/kg/day, flucytosine modestly reduced counts of *C. tropicalis* in the spleen. Although the actual median counts were close to those for flucytosine, neither fluconazole nor D0870 had any significant benefit at dosages of 0.2 mg/kg/day for D0870 and 0.5 mg/kg twice daily for fluconazole. Flucytosine sharply reduced the renal tissue counts. The combination of flucytosine and fluconazole or D0870 was not superior to flucytosine alone.

DISCUSSION

These studies examined multiple therapeutic regimens in neutropenic mice infected with four different isolates of *C. tropicalis*. Our initial anticipation was that *C. tropicalis* would be consistently more resistant than *C. albicans* to antifungal therapy but that combined treatment with azole and flucytosine would be advantageous, as we have shown for *Cryptococcus neoformans* infection (1). However, this did not prove to be the case.

All four isolates were very susceptible in vitro to flucytosine. Flucytosine was regularly effective in vivo as a single drug down to dosages as low as 60 mg/kg/day, and in some studies, it was effective to a dosage as low as 20 mg/kg/day. For isolate 510, results with flucytosine were not internally consistent from

TABLE 4. Survival of mice infected with fluconazole-resistant *C. tropicalis* and treated with fluconazole, flucytosine, or D0870

Isolate	Drug[a]	Dosage (mg/kg/day)[b]	Mean survival (days) ± SE	% Mortality at day 30
168				
Study 1	None		4 ± 0.4	100
	Flucytosine	20 in H_2O	6 ± 0.5	100
	Fluconazole	0.1 BID	4 ± 0.2	100
	Fluconazole + flucytosine	0.1 BID + 20 in H_2O	7 ± 2.1	100
	D0870	0.2	4 ± 0.3	100
	D0870 + flucytosine	0.2 + 20 in H_2O	5 ± 0.6	100
Study 2	None		9 ± 0.6	100
	Flucytosine	40 in H_2O	26 ± 2.9[c]	30
	Fluconazole	0.5 BID	14 ± 1.1[c]	100
	Fluconazole + flucytosine	0.5 BID + 40 in H_2O	29 ± 1.5[c]	20
	D0870	0.5	20 ± 3.1[c]	60
	D0870 + flucytosine	0.5 + 40 in H_2O	30 ± 0.8[c]	20
Study 3	None		11 ± 3.4	80
	Flucytosine	120 in H_2O	24 ± 3.4[c]	40
	Fluconazole	0.5 BID	12 ± 3.1	90
	Fluconazole + flucytosine	0.5 BID + 120 in H_2O	18 ± 3.3	70
	D0870	1.0	29 ± 1.8[c]	10
	D0870 + flucytosine	1.0 + 120 in H_2O	18 ± 4.0	70
Study 4	None		13 ± 3.8	90
	Flucytosine	240 in H_2O	27 ± 5.1[c]	60
	Fluconazole	2.5 BID	36 ± 4.5[c]	30
	Fluconazole + flucytosine	2.5 BID + 240 in H_2O	46 ± 0[d]	0
	D0870	10 on alternate days	46 ± 0[c]	100
	D0870 + flucytosine	10 on alternate days + 240 in H_2O	44 ± 2.4[c]	10
Study 5	None		4 ± 0.4	100
	Flucytosine	80 TID	29 ± 5.4[c]	60
	Fluconazole	15 BID	35 ± 5.5[c]	30
	Fluconazole + flucytosine	15 BID + 80 TID	19 ± 4.9[c]	80
	D0870	30	35 ± 4.9[c]	60
	D0870 + flucytosine	30 + 80 TID	29 ± 6.3[c]	50
231				
Study 1	None		12 ± 3.3	80
	Flucytosine	60 in H_2O	26 ± 2.7[c]	30
	Fluconazole	0.1 BID	7 ± 0.4	100
	Fluconazole + flucytosine	0.1 BID + 60 in H_2O	24 ± 3.5	40
	D0870	0.2	9 ± 2.6	90
	D0870 + flucytosine	0.2 + 60 in H_2O	21 ± 3.3	60
Study 2	None		6 ± 0.4	100
	Flucytosine	60 in H_2O	27 ± 2.0[c]	40
	Fluconazole	0.5 BID	9 ± 1.1	100
	Fluconazole + flucytosine	0.5 BID + 60 in H_2O	21 ± 2.2[c]	70
	D0870	0.2	7 ± 0.4	100
	D0870 + flucytosine	0.2 + 60 in H_2O	24 ± 2.4[c]	50
Study 3	None		14 ± 2.6	90
	Flucytosine	120 in H_2O	28 ± 2.6[c]	20
	Fluconazole	0.5 BID	20 ± 2.8	70
	Fluconazole + flucytosine	0.5 BID + 120 in H_2O	30 ± 1.1[c]	80
	D0870	1.0	31 ± 1.3[c]	10
	D0870 + flucytosine	1.0 + 120 in H_2O	31 ± 1.2[c]	20
Study 4	None		7 ± 0.3	100
	Flucytosine	240 in H_2O	31 ± 5.0[c]	50
	Fluconazole	2.5 BID	8 ± 0.4	100
	Fluconazole + flucytosine	2.5 BID + 240 in H_2O	32 ± 4.8[c]	50
	D0870	10 on alternate days	35 ± 5.9[c]	30
	D0870 + flucytosine	10 on alternate days + 240 in H_2O	43 ± 2.1[c]	10
Study 5	None		12 ± 3.8	90
	Flucytosine	80 TID	26 ± 4.4[c]	70
	Fluconazole	15 BID	32 ± 6.0	40
	Fluconazole + flucytosine	15 BID + 80 TID	33 ± 5.8	40
	D0870	30	40 ± 2.6[c]	30
	D0870 + flucytosine	30 + 80 TID	39 ± 4.6[c]	20

[a] Note that no combination was superior to either drug individually except as noted.
[b] Abbreviations: BID, twice a day; TID, three times a day.
[c] Treatment superior to control.
[d] Combination superior to either drug individually.

TABLE 5. Tissue counts for mice with disseminated *C. tropicalis* isolate 231

Drug[a]	Drug dosage (mg/kg/day)	Tissue counts (CFU/g [10^5])		
		Median	Range	
			Lower	Upper
Spleen				
None		1.7	0.5	8.3
Flucytosine	60 in H_2O	0.7	0.2	1.3
Fluconazole	0.5 BID[b]	0.9	0.4	50
Fluconazole + flucytosine	0.5 BID + 60 in H_2O	1.0	0.3	8.5
D0870	0.2	1.9	0.05	391
D0870 + flucytosine	0.2 + 60 in H_2O	0.6	0.2	1.6
Kidney				
None		4,530	305	6,130
Flucytosine	60 in H_2O	82[c]	23	1,330
Fluconazole	0.5 BID	3,860	505	37,200
Fluconazole + flucytosine	0.5 BID + 60 in H_2O	296[c]	72	12,600
D0870	0.2	24,300	24	86,200
D0870 + flucytosine	0.2 + 60 in H_2O	75	7	3,050

[a] Note that no combination reduced counts significantly below that of either drug individually.
[b] BID, twice a day.
[c] Treatment reduced the count significantly below that of control.

study to study. In study 1 a low dosage of 20 mg/kg/day was effective, but 80 mg/kg three times a day and 120 mg/kg/day in water were not significantly effective. These results remain unexplained. Flucytosine results were consistent in studies of other isolates. Because the addition of flucytosine at these doses did not negate the survival benefit conferred by fluconazole or D0870 and because in the other three isolates similarly high doses of flucytosine in water did prolong survival over that of controls, we do not think that toxicity from the high dose of flucytosine played a role.

Responses to fluconazole were generally consistent in studies of each isolate, and each showed a response beginning at twice-daily doses of 0.5 mg/kg (isolates 681 and 168) and 2.5 mg/kg (isolate 510). There was no fluconazole response in isolate 231. Some isolates, such as 681 and 168, had a significant result at 0.5 mg/kg in one study and an insignificant prolongation of survival in a repeat study. This may be because the dosage was just at a critical level. This in vivo responsiveness to fluconazole did not agree with the in vitro susceptibilities in that one resistant isolate was highly responsive, while one susceptible isolate showed slightly more resistance than the other susceptible isolate.

D0870 was of a potency generally similar to that of fluconazole, except that the dose could be given once a day, and in all studies, D0870 was effective when given on alternate days. For isolate 168, 0.5 mg/kg/day was effective; for isolates 510 and 231, 1 mg/kg/day was effective; and for isolate 681, 10 mg/kg given on alternate days was effective.

Unfortunately, in only one study did the addition of flucytosine to either fluconazole or D0870, over a very broad dose range of azoles and flucytosine, prolong survival significantly more than flucytosine, fluconazole, or D0870 given alone. The results of combination therapy were in general similar to those with the better of the individual drugs. It is possible that our dosing regimens of flucytosine, which varied from 20 to 240 mg/kg/day, administered constantly or intermittently, might not have hit upon some specific combination that provides significant benefit over either drug alone. However, we believe that it is very unlikely that we missed a putative optimal combination. Tissue count studies indicated an additive effect of combination flucytosine-triazole therapy in spleen and kidney counts of isolate 681, noted for both fluconazole and D0870. More extensive studies of reduction of tissue counts might have shown other additive results, but these are very labor-intensive and were not pursued in view of the generally negative survival studies and limitation of benefit to the much more lightly infected spleen tissue. Therefore, if a narrowly defined set of dosing parameters could have identified a consistent additive effect of flucytosine upon the azoles, the clinical applicability would still be unclear.

There are inherent limitations in murine studies of pharmacotherapy. A major one is the great differences among drug clearances in mice and humans. Because it is cleared much more rapidly than D0870, fluconazole was administered twice daily, and D0870 was given either once daily or on alternate days (3, 7). We compared efficacies in terms of total daily dose, and by this parameter, both fluconazole and D0870 appeared similarly potent.

These studies thus extend comparisons of fluconazole and D0870 to *C. tropicalis*, a non-*albicans* species which has been reported relatively resistant to fluconazole in vitro. However, with *C. tropicalis*, in vitro susceptibilities did not predict in vivo response to fluconazole in all of the isolates, as reported by Karyotakis et al. (8) for *C. albicans* strains sensitive or resistant in vivo to fluconazole. Our results are encouraging for fluconazole, which was effective at doses similar to those for *C. albicans* in mice. None of our isolates was resistant to either flucytosine or D0870, so no comparisons of in vitro and in vivo responses are possible. There is one note of caution in that neither of the isolates studied for tissue count reductions showed any benefit for D0870 in kidneys. D0870 is excreted by nonrenal mechanisms, and it is possible that this drug might not be effective in renal candidiasis. In summary, both fluconazole and D0870 appear effective at prolonging survival at low doses in disseminated C. tropicalis infection, but addition of flucytosine does not augment the effect of either triazole.

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