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Comparison of Oral Fluconazole and Clotrimazole Troches as Treatment for Oral Candidiasis in Patients Infected with Human Immunodeficiency Virus

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Thirty-nine adult patients with human immunodeficiency virus infection and oral candidiasis were randomly assigned to receive either one fluconazole capsule (100 mg) or five clotrimazole troches (10 mg each) daily for 14 days. Among 36 evaluable patients, clinical resolution rates were 100 and 65%, respectively ($P = 0.018$). Mycological eradication rates were 75 and 20%, respectively ($P = 0.004$). Fluconazole-treated patients were more likely to remain disease free during follow-up than those treated with clotrimazole ($P = 0.014$ at 2 weeks). Prolonged clinical responses correlated with mycological eradication at the end of therapy ($P = 0.043$).

Fluconazole is a new bis-triazole antifungal agent with good bioavailability, low protein binding, a volume of distribution which approximates total body water, and a long serum half-life (5). Favorable results have been obtained by using fluconazole as a treatment for oropharyngeal candidiasis both in noncomparative studies (1, 3; P. R. Farrow, K. W. Brammer, and J. M. Feczko, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 949, 1987) and in comparison with ketoconazole (2). In this paper, we report the results of a prospective, randomized trial comparing the efficacy (both clinical and mycological) of and the tolerance to fluconazole with the efficacy of and tolerance to clotrimazole troches in the management of oropharyngeal candidiasis in patients infected with human immunodeficiency virus (HIV).

After giving their informed consent, 39 patients, ages 22 to 43 years (mean, 33 years), with documented HIV infection and oral candidiasis were randomly assigned to 14 days of treatment with either one capsule (100 mg) of fluconazole daily or one clotrimazole troche (10 mg) five times daily. Diagnosis of thrush was based on typical signs and symptoms and was confirmed by KOH examination and fungal cultures. Disease was categorized as mild, moderate, or severe depending on the extent of erythema, the number of plaques, and the degree of oral discomfort. The importance of compliance was emphasized to all patients.

Selected characteristics of the 39 patients enrolled in the study are shown in Table 1. Seventeen of the 19 patients randomly selected to receive fluconazole were evaluable; two patients were excluded, one who never received any drug and another who was found to meet an exclusion criterion after enrollment. Nineteen of the twenty patients randomly selected to receive clotrimazole troches were evaluable; one patient was excluded because he had moved prior to the first evaluation and his case could not be followed up. Both treatment groups were comparable in the degree of immunosuppression, concurrent zidovudine therapy, and antifungal therapy within the preceding 3 months. Likewise, both groups showed similar distributions in the severity of disease at the time of entry.

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During the active treatment phase of the study, patients were evaluated at days 3, 7, and 14 for evidence of disease, side effects, or both. Fungal cultures were obtained before treatment and on days 7 and 14 by plating swabs from affected areas of the oropharynx onto each of the following media: potato flakes agar (4) with and without gentamicin and chloramphenicol, brain heart infusion agar with gentamicin and cycloheximide (Difco Laboratories, Detroit, Mich.), and yeast extract agar (Difco Laboratories). Culture plates were read daily for the first week and twice weekly for the ensuing 3 weeks. Patients who were clinically disease free at the end of therapy were evaluated for clinical relapse at 2 and 4 weeks posttherapy (days 28 and 42). Clinical responses were defined as resolution or failure (persistence or relapse). Mycological responses were determined by culture results obtained at the end of therapy and were categorized as either eradication (no growth) or failure (any growth). Statistical analyses of results were performed with the two-tailed Fisher's exact test.

The clinical and mycological responses during treatment are summarized in Table 2. Of the evaluable patients, one in the fluconazole group was withdrawn from study between days 7 and 14 because he was found to have an excludable condition. Two patients in the clotrimazole group did not return on days 3 and 7 for evaluation, but both were evaluated at the end of the study; two others were withdrawn from the study between days 7 and 14 because of drug intolerance. After 14 days of therapy, fluconazole was clinically more efficacious and resulted in significantly better mycological eradication than clotrimazole.

None of the patients in the fluconazole group, compared with six patients in the clotrimazole group, were considered therapeutic failures at the end of treatment. Of the six clinical failures, two were improved but had persistent lesions, one showed no demonstrable change, two had initial clearing but relapsed, and one had progressive lesions during therapy.

Posttherapy follow-up of the patients who had clinical resolution during treatment is shown in Table 3. Excluded are one fluconazole patient who died from an intercurrent illness early in the follow-up period and four clotrimazole patients who did not return for posttherapy evaluations. Fluconazole-treated patients were more likely to remain

TABLE 1. Characteristics of study population

Characteristic	No. of patients treated with:	
	Fluconazole	Clotrimazole
Random assignment	19	20
Evaluability	17	19
Male	17	16
CD4 counts (cells/mm^3)		
<200	15	16
200–500	2	3
Concurrent zidovudine	5	4
Previous antifungal agents	7	6
Severity of disease		
Mild	10	9
Moderate	6	9
Severe	1	1

disease free during follow-up than those treated with clotrimazole ($P = 0.014$ at day 28). Eight of twelve patients (four in each treatment group) who had positive cultures at the end of therapy had relapsed by day 42. In contrast, negative cultures were obtained from 8 of the 10 patients (8 of 9 taking fluconazole and 0 of 1 taking clotrimazole) who remained disease free 4 weeks posttherapy ($P = 0.043$).

There were no serious side effects in either group. Nausea was the major subjective complaint and occurred in three patients in each group. In two of the three clotrimazole-treated patients, this nausea, along with altered taste sensations, resulted in premature discontinuation of therapy.

Complete blood counts including leukocyte differential and platelets, prothrombin time, blood urea nitrogen, creatinine, total bilirubin, and liver enzymes (aspartate transaminase, alanine transaminase, gamma-glutamyl-transpeptidase, and alkaline phosphatase) were drawn at baseline. Follow-up laboratory tests were performed on days 7 and 14 of therapy to detect any potential toxicities. One patient in each treatment group had moderate elevations of liver enzymes, a condition which may have been drug-related.

Compliance with treatment regimens was assessed by counting the number of pills returned at each evaluation point during the treatment period. Patients taking fluconazole (one capsule daily) were uniformly compliant. Only two patients in the clotrimazole group, however, completely followed the treatment regimen (one troche five times daily) for the full 14 days as prescribed. The average number of troches missed by these patients throughout the study period was 6 (range, 3 to 12) of 70 prescribed. The patient who was deemed an early failure because of worsening disease actually took more than the prescribed five troches per day prior to discontinuation. Reasons for noncompliance included forgetfulness, the inconvenience of taking multiple doses, and altered taste sensations.

TABLE 2. Response during treatment period

Study day and type of evaluation	No. resolved/no. evaluated (%)[a]		*P* value
	Fluconazole	Clotrimazole	
3			
Clinical	7/17 (41)	9/17 (53)	0.732
Culture	ND	ND	
7			
Clinical	17/17 (100)	13/17 (76)	0.103
Culture	8/17 (47)	7/16 (44)	1.000
14			
Clinical	16/16 (100)	11/17 (65)	0.018
Culture	12/16 (75)	3/15 (20)	0.004

[a] ND, Not done.

TABLE 3. Clinical outcome at follow-up of patients who had clinical resolution during treatment period

Study day	No. resolved/no. evaluated (%)		*P* value
	Fluconazole	Clotrimazole	
28	13/15 (87)	2/7 (29)	0.014
42	9/15 (60)	1/7 (14)	0.074

This study showed that fluconazole was more effective than clotrimazole troches in the treatment of HIV-infected patients with oral candidiasis. Prolonged clinical responses following 14 days of therapy were related, at least in part, to better mycological eradication, although previous studies have not shown such a relationship (1, 2). Better compliance and tolerance of fluconazole also might have accounted for some of its superior efficacy. The documented efficacy of fluconazole, its ease of administration, and the overall high tolerance of patients to it make this drug an attractive alternative for the treatment of oropharyngeal candidiasis in the HIV-infected population. The exact dosage, the duration of therapy, and the need for maintenance therapy still need to be defined. In individual patients, tolerance of topical agents, severity of disease, and cost should be important considerations in drug choice.

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