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Fluconazole in the Treatment of *Candida*-Associated Denture Stomatitis

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A double-blind trial was carried out to study the effect of oral administration of fluconazole in the treatment of *Candida*-associated denture stomatitis. The study group consisted of 38 denture stomatitis patients who harbored yeasts, predominantly *Candida* spp., in significant numbers as determined by culture from the lesions. Half of the patients received 50 mg of fluconazole per day orally for 14 days, and the other half received placebo capsules. The following parameters were studied: degree of palatal erythema, presence of yeast cells (by plate count and microscopy of smears), identification to the species level of dominant yeast organisms, biotyping of *Candida albicans*, and treatment-related side effects. A significant reduction of erythema was seen after treatment with fluconazole, but the inflammation showed partial relapse 2 to 4 weeks after treatment was terminated. Reduced soreness of the oral mucosa was reported by six of the patients in the fluconazole group. No significant clinical or yeast flora changes were observed in the placebo group. Extensive changes in the yeast flora were observed in the fluconazole group, both in quantity and in composition of yeast species and *C. albicans* strains (biotypes), which perhaps indicated differences in pathogenicity and fluconazole susceptibility among various yeast species and *C. albicans* strains. Fluconazole did not produce any changes in the results of blood and urine analyses. The results indicate that fluconazole is a safe and well-tolerated antimycotic drug. The transient clinical and antimycotic effect may have been due in part to the possibility that therapeutic concentrations of the drug were not reached beneath the fitting denture surface and within the denture plaque.

Candida-associated denture stomatitis is characterized by generalized inflammation of the palatal mucosa covered by a denture (6, 7). The condition is a very common and usually harmless form of oral candidiasis and is associated with a quantitative increase of yeasts, particularly *Candida albicans*, on the mucosa and the fitting denture surface (10). Invasive infection by the yeast cells into the oral mucosa is seen very seldom since the cells are present within the denture plaque and on the surface of the denture-covered mucosa (12, 24). The presence of numerous yeasts may give rise to spreading to the angles of the mouth, the tongue, the pharynx, and the alimentary and respiratory tracts. Furthermore, in patients with reduced salivary secretion, yeast infection may become extensive and give rise to severe itching and burning pain from the oral mucosa (21). The lesions usually heal after topical antifungal treatment as the yeast counts of the denture plaque are suppressed (11, 12, 23). The incidence of relapse of *Candida*-associated denture stomatitis is, however, very high (6; T. Bergendal, thesis, Stockholm, Sweden, 1982).

Fluconazole (UK-49,558) is a new oral bis-triazole antifungal drug which is effective against a range of experimentally induced fungal infections in animals (15, 20, 25). Furthermore, fluconazole has been shown to be effective in the treatment of vulvovaginal candidiasis (5). The purpose of this investigation was to study the effect and tolerance for fluconazole in the treatment of *Candida*-associated denture stomatitis.

MATERIALS AND METHODS

Study group. The study group consisted of 38 denture wearers with denture stomatitis yielding yeasts by isolation from the fitting denture surface and the palatal mucosa. The patients were assigned randomly to a fluconazole or a placebo group. Distributions of the patients according to sex, age, and weight were comparable for the two groups. The fluconazole group consisted of 11 females and 8 males with a mean age of 59.8 years (range, 45 to 65 years) and a mean weight of 68.0 kg (range, 51 to 91 kg). The placebo group contained 11 females and 8 males with a mean age of 58.9 years (range, 38 to 65 years) and a mean weight of 73.6 kg (range, 50 to 130 kg). Excluded from the study were females of child-bearing age, patients with impaired hepatic or renal function, and patients who had received any recent treatment with antifungal agents. The protocol for the study was approved by the local ethical review committee, and all patients gave informed consent to participate in the study. The study was carried out as a double-blind study.

At the initial visit, the fitting denture surface and the palatal mucosa were examined for yeasts by cultivation on candida BCG medium followed by plate counting. Patients whose cultures yielded ≥100 yeast colonies per plate and who fulfilled the other requirements for participating in the study had blood and urine samples taken at a subsequent visit for routine hematologic examinations and tests of hepatic and renal functions (see below). Patients whose values were within the normal range were allocated to treatment with fluconazole or placebo according to a predetermined randomization list. They received one daily capsule for 14 days of either fluconazole (50 mg) or placebo to be swallowed, preferably with a meal. Clinical and mycological investigation was conducted before and immediately after treatment and 2 and 4 weeks after treatment was terminated. Blood and urine samples were also obtained immediately after treatment for the same laboratory tests as were carried out at base line to detect possible toxic effects of treatment.

Clinical investigation. The clinical effect of treatment was monitored by scoring the degree of palatal erythema as 0 (no

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TABLE 1. Clinical efficacy of treatment evaluated by mean scores for signs and symptoms associated with denture stomatitis[a]

Time of scoring	Sign or symptom	Fluconazole		Placebo	
		Mean score	No. of patients evaluated	Mean score	No. of patients evaluated
Base line	Inflammation	2.3	19 (19)[b]	2.2	19 (19)
	White patches	1.0	5 (5)	1.0	2 (2)
	Angular cheilitis or glossitis	1.5	6 (6)	1.8	9 (10)
	Soreness	1.4	9 (9)	1.3	4 (4)
End of treatment	Inflammation	1.1	16 (19)	2.2	19 (19)
	White patches	0	0 (5)	0	2 (2)
	Angular cheilitis or glossitis	0.7	3 (6)	1.5	9 (10)
	Soreness	0.4	3 (9)	1.0	4 (4)
Follow-up					
2 wk	Inflammation	1.5	17 (19)	2.0	18 (19)
	White patches	0.4	1 (5)	0.5	1 (2)
	Angular cheilitis or glossitis	0.6	2 (6)	1.5	8 (10)
	Soreness	0.6	3 (9)	0.8	3 (4)
4 wk	Inflammation	1.8	18 (19)	2.1	19 (19)
	White patches	0.6	2 (5)	0.5	1 (2)
	Angular cheilitis or glossitis	0.7	3 (6)	1.5	8 (10)
	Soreness	0.9	4 (9)	0.5	2 (4)

[a] 0, Absent; 1, mild; 2, moderate; 3, severe.
[b] Numbers in parentheses are numbers of patients in whom the indicated sign or symptom was present at least once during the study.

inflammation), 1 (slight inflammation), 2 (moderate inflammation), or 3 (severe inflammation) (7). Furthermore, pre- and posttreatment photographs of the palatal mucosa as well as lesions in other sites of the oral mucosa were compared (investigator assessment), and the clinical effect was graded as cured (inflammation resolved), improved (inflammation reduced), or failure (no change) (7).

Mycological investigation. Swabs were used to collect yeast samples from the fitting denture surface and the underlying palatal mucosa. After inoculation on candida BCG medium, the cultures were incubated at 35°C for 2 to 3 days. Colony counts were made according to the following scale to obtain the yeast score: 0 (no growth), 1 (less than 10 colonies per plate), 2 (between 10 and 100 colonies per plate), 3 (more than 100 colonies per plate), and 4 (confluent growth).

To identify the yeasts, the microorganisms were subcultured on candida BCG medium to obtain pure culture. Identification to the species level was based on performance on morphology media for development of chlamydospores and pseudohyphae as well as on assessment of utilization of carbon and nitrogen sources by the auxanographic method. The isolated *C. albicans* strains were further identified to the biotype level by the Leicester procedure (18, 19).

Smears were obtained from the palatal mucosa and the fitting denture surface. The smears were fixed in isopropyl alcohol and stained by the periodic acid-Schiff method for identification of yeast cells (blastospores, hyphae, and pseudohyphae); the concentration of yeast cells was recorded by using the following scale: − (no yeast cells present), +, (single hypha or pseudohypha present), ++ (a few hyphae or pseudohyphae present in several microscopic fields), and +++ (several hyphae or pseudohyphae present in several microscopic fields).

Safety tests. Possible side effects, time of onset, duration, and any symptomatic treatment required were recorded after treatment and at both follow-up visits. Laboratory safety tests conducted before and immediately after treatment consisted of hemoglobin, hematocrit, erythrocyte, platelet, and total and differential leukocyte counts; serum aspartate aminotransferase, serum alanine aminotransferase, serum bilirubin, and serum phosphatase; urea creatinine, nitrogen, cholesterol, protein, and glucose; and microscopy of spun urine deposits when appropriate. The tests were carried out by Medical Laboratory Inc., Copenhagen, Denmark.

Statistical methods. Differences in yeast and inflammation scores after treatment with fluconazole and placebo were tested for statistical significance (Wilcoxon rank sum test) after termination of treatment and after the first and second follow-up examinations. Differences between treatment groups in clinical cure and improvement rates as reported by the investigator were tested for significance by the chi-square test. $P < 0.05$ was considered indicative of a significant difference.

RESULTS

Clinical investigation. Mean scores for symptoms and signs recorded at base line, after treatment, and at 2- and 4-week follow-ups are given in Table 1. Inflammation was reduced in the fluconazole group from a mean score of 2.3 at base line to 1.1 at the end of treatment, whereas no change in score occurred in the placebo group. This difference between the groups was statistically significant ($P < 0.001$). At the 2-week follow-up examination, the difference in inflammation scores between the two groups was still statistically significant. At the 4-week follow-up, however, there was no difference between the groups.

Reduction in scores for white patches, soreness, and angular cheilitis were observed in the fluconazole group only (Table 1). However, there were various degrees of relapse by the 4-week follow-up examination. Three patients with erythema of the soft palate and three patients with white lesions on the tongue still showed normalization of the previously affected areas at the 4-week follow-up examination, although there was complete relapse of the lesions of the palate.

According to the investigator assessment, 89% of the fluconazole group responded to treatment (16% cured and 73% improved), whereas none of the patients in the placebo

TABLE 2. Investigator assessment of clinical response to treatment

Assessment	No. (%) of patients		P^a
	Fluconazole	Placebo	
End of treatment			
Cure	3 (16)	0 (0)	<0.001
Improvement	14 (73)	0 (0)	
Failure	2 (11)	19 (100)	
2-wk follow-up			
Cure	2 (11)	0 (0)	0.003
Improvement	8 (42)	0 (0)	
Failure	9 (47)	18 (100)	
4-wk follow-up			
Cure	1 (5)	0 (0)	0.02
Improvement	4 (21)	0 (0)	
Failure	14 (74)	19 (100)	

[a] Significance level of difference between treatment groups tested by the chi-square test (2 df).

group responded (Table 2). At 2- and 4-week follow-up examinations, the number of patients who had responded to fluconazole gradually declined, but the difference between the groups was still statistically significant.

Mycological investigation. The total mycological cure rates were low in the fluconazole group (3 of 19), but the yeast score was reduced. At termination of treatment, the yeast score of the fluconazole group was significantly lower than that of the placebo group (Table 3). At the 4-week follow-up examination, the yeast score was at the same level as the base-line yeast score. There was also a significant reduction in the concentration of yeast cells in oral smears in the fluconazole group compared with the placebo group (Fig. 1). At the 2-week follow-up examination, the two groups did not differ significantly with respect to the number of yeast cells in oral smears.

The species compositions of the yeast flora in the two groups of patients were identical, with *Candida* spp. making up about 80% of all yeasts isolated and *C. albicans* being by far the dominating species, accounting for about 70% of the 114 isolated yeast organisms (Table 3). In the placebo group, there was no change, either quantitatively (Table 4) or in species composition, in the yeast flora during the entire study period. Thus, for each patient the same species and, for *C. albicans*, the same strains (biotypes) were present throughout the entire period. In contrast, pronounced alterations of the yeast flora were observed in the fluconazole group. In one patient *C. albicans* was eradicated completely, an event accompanied by improved clinical status. In two patients the original yeast species was eradicated and substituted by *Saccharomyces* sp., accompanied by an improved clinical status or intermittent cure. In most cases, however, the originally observed organisms were eradicated and substituted by other known pathogenic yeasts, either a different species or, in the case of *C. albicans*, another strain of the same species as determined by the biotyping procedure; in all patients, these findings were accompanied by an intermittently improved clinical status. In two patients showing no clinical effect at all, the same *C. albicans* strain was present throughout the study period. In five patients the same *C. albicans* strain was found throughout the study period, generally accompanied by an intermittently improved clinical status. Surprisingly, in the only patient with a complete cure, the same *C. albicans* strain persisted throughout the study period.

TABLE 4. Taxonomic distribution of 114 yeast isolates from palatal mucosa[a]

Yeast species	% of patients with isolate		
	Fluconazole group	Placebo group	All patients
Candida albicans	68.4	70.6	69.5
Candida tropicalis	8.9	10.6	9.8
Candida sp.	2.5	1.2	1.8
Torulopsis glabrata	11.4	11.8	11.6
Saccharomyces sp.	7.6	2.4	4.9
Yeast cells not identified	1.3	3.5	2.4

[a] Of the total 114 isolates, 54 were from the fluconazole group and 60 were from the placebo group.

Safety and tolerance. Mild, uncharacteristic, and transient symptoms (dizziness, nausea, and dry mouth) were reported by eight patients in each of the two groups. Liver function tests showed no consistent changes after treatment with fluconazole. Similarly, metabolic and renal function tests were not affected by treatment with fluconazole. There were no signs that fluconazole caused any hematologic changes.

DISCUSSION

Variable results have been observed after topical treatment with antimycotic drugs in patients with *Candida*-associated denture stomatitis. After topical treatment with amphotericin B, nystatin, or pimaricin, improvement of mucosal inflammation and suppression of yeast growth are usually seen (4, 6, 11, 16; Bergendal, thesis, 1982). However, the incidence of relapse of infection is significant shortly after treatment is terminated (6; Bergendal, thesis, 1982). Recently it was shown that mechanical cleansing of dentures was as efficient as topical treatment with amphotericin B in treating *Candida*-associated denture stomatitis, and it was concluded that routine prescription of antimycotic drugs was unnecessary for treating this condition (26). However, anti-

TABLE 3. Mean yeast scores

Time of scoring	Fluconazole		Placebo		Difference	
	Mean score[a] (SE)	No. of patients	Mean score (SE)	No. of patients	Mean score (SE)	P
Before treatment	2.63 (0.21)	19	2.84 (0.19)	19	−0.21 (0.25)	NS[b]
End of treatment	1.37 (0.29)	19	2.68 (0.20)	19	−1.35 (0.35)	0.001
Follow-up						
2 wk	2.17 (0.31)	18	2.60 (0.27)	15	−0.43 (0.41)	NS
4 wk	2.53 (0.22)	19	2.67 (0.26)	18	−0.14 (0.35)	NS

[a] Scoring: 1, fewer than 10 colonies; 2, 10 to 100 colonies; 3, >100 colonies; 4, confluent growth.
[b] NS, Not significant.

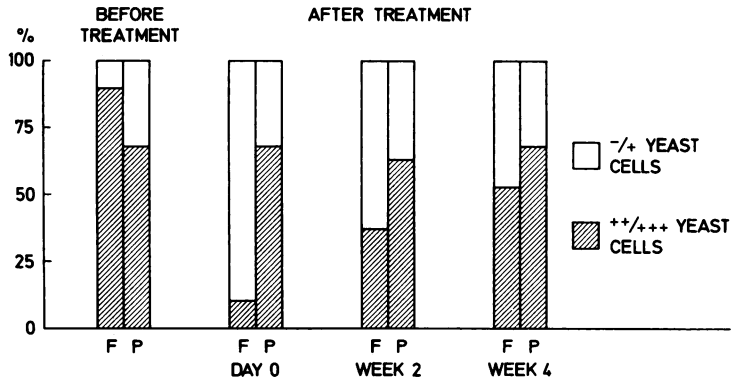

FIG. 1. Concentration of yeast cells in oral smears in the fluconazole group (F) and the placebo group (P) before and immediately after treatment and 2 and 4 weeks after treatment was terminated. −, No yeast cells; +, single hypha or pseudohypha; ++, a few hyphae or pseudohyphae present in several microscopic fields; +++, several hyphae or pseudohyphae present in several microscopic fields.

fungal therapy may be indicated for patients with severe and painful denture stomatitis and for treatment of infections that tend to spread (6).

This study showed that fluconazole was a well-tolerated antimycotic drug which caused no consistent changes of liver, renal, or metabolic function tests and which produced only mild and transient symptoms. The yeast floras of the placebo and fluconazole groups were comparable before treatment in terms of both the concentration of yeast cells and the composition of species and *C. albicans* biotypes. The yeast floras were also similar to those encountered in other yeast-associated lesions of the oral mucosa (17).

Not surprisingly, the yeast flora in the placebo group did not change during the study period. In the fluconazole group, however, a marked suppression of the concentration of yeast cells on the fitting denture surface and the palatal mucosa was observed, and the inflammation was reduced. Furthermore, extensive changes in the yeast flora occurred, which indicated that the drug had been used by the patients, was present on the mucosal surface beneath the denture, and was affecting the yeast organisms. The fact that several patients showed a relatively poor response to treatment with fluconazole may have been because the treatment period was too short, the concentration of fluconazole in the denture plaque was too low, or bacteria contributed to the infection.

The effect of the drug on the yeast flora consisted of eradication of the original yeast organism or, more commonly, of substitution of the original organism by other species or other *C. albicans* strains. When the extensive mycological events were compared with the clinical parameters, no obvious correlation was apparent. Two factors can be suggested as possible explanations: (i) the susceptibilities to fluconazole of various yeast species and yeast strains differ, and (ii) the pathogenicities of strains within the species *C. albicans*, *Candida tropicalis*, and *Torulopsis glabrata* differ.

Differences in the susceptibilities of various yeasts to drugs have been reported (2). In fact, a few *C. albicans* strains exhibiting fluconazole resistance have been encountered, and concern has been expressed that primary imidazole resistance in *C. albicans* may not be rare (22). Strain differences in pathogenicity within the species *C. albicans* and *C. tropicalis* have been reported, also in relation to oral candidiasis, based on animal experiments (1, 27). But this issue has so far not been studied in relation to *Candida*-associated denture stomatitis.

Fluconazole is well absorbed after oral administration, and peak concentrations in plasma are obtained about 2 h after intake of the drug (S. Jevons and M. H. Tarbit, Abstr. 9th Int. Congr. Soc. Hum. Anim. Mycoses, abstr. no. 2-3, 1985). The drug is eliminated slowly and has a half-life in plasma of 25 h. Determination of concentrations of fluconazole in human saliva after oral intake of the drug has shown that the concentration of fluconazole in saliva is similar to that in plasma (13). Although fluconazole had a marked clinical effect, infection was reestablished 2 to 4 weeks after treatment was terminated. This result indicated that a daily dose of 50 mg of fluconazole for 2 weeks was not more efficient than topical treatment with antimycotic drugs for a similar treatment period (3, 9, 11).

There are several explanations of why the clinical and antimycotic effects of fluconazole were only temporary. First, substitution or reinfection may have occurred via supply of new organisms from exogenous sources, particularly food. Second, the concentration of fluconazole may not have been high enough to eradicate yeasts within the denture plaque, since a close-fitting denture could cut off free salivary flow. This possibility is supported by the fact that candidal lesions outside the denture-bearing mucosa, i.e., the tongue, soft palate, and angles of the mouth, did not show relapse during the 4-week posttreatment observation period.

In this study, no special attention was paid to the oral and denture hygiene of the patients. Therefore, the denture and the underlying mucosa could easily have been recolonized by yeasts after withdrawal of antimycotic treatment. To obtain a more long-lasting cure after antifungal therapy, meticulous hygienic care of the dentures and the oral mucosa is important (6; Bergendal, thesis, 1982). However, fluconazole would be advantageous for use in patients suffering from *Candida*-associated denture stomatitis and concomitant infections of other mucosal sites by *Candida* spp. In these instances, treatment with fluconazole should be combined with immersion of the dentures in chlorhexidine or an enzyme denture cleanser (8, 9) and efficient oral and denture hygiene.

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