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Efficacy of the Cyclodextrin Liquid Preparation of Itraconazole in Treatment of Denture Stomatitis: Comparison with Itraconazole Capsules

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This study investigated the efficacy of a cyclodextrin solution of itraconazole in the treatment of *Candida*-associated denture stomatitis. It was found that the liquid and capsule preparations of itraconazole were equally effective adjuncts in the treatment of this condition. However, the side effect profile indicates that capsules are the preferred formulation.

The systemic antifungal agent itraconazole is dispensed as a lactose bead-encapsulated preparation and, more recently, as a liquid formulation based on hydroxy-β-cyclodextrin. This new cyclodextrin solution of itraconazole may provide a major therapeutic advantage over traditional treatment of oral candidosis as it combines the effect of topical application to the oral mucosa and systemic activity after absorption (5).

Forty edentulous patients whose palatal and tongue swab specimens were culture positive for yeasts were enrolled in a parallel-design, single-blind clinical trial. Demographic details and a full medical and dental history were obtained from each participant. An oral examination was performed, and denture stomatitis was classified according to the method of Newton (13). Palatal erythema was assessed visually (7) and measured objectively by using an electro-optical instrument known as an erythema meter (9). Denture-fitting surfaces were given a visual denture cleanliness score (4). Imprint cultures (4) of the palate, tongue, and upper denture, an oral rinse specimen, and a denture disc specimen were collected for microbiological examination. Blood was taken for routine hematological and biochemical analyses. All participants were given both verbal and written denture hygiene instructions.

The patients were randomized to receive either a cyclodextrin solution of itraconazole (Sporanox Liquid; Janssen-Cilag Ltd., High Wycombe, United Kingdom) or itraconazole capsules (Sporanox; Janssen-Cilag Ltd.), both at a dose of 100 mg twice daily for 15 days. Patients were reviewed on completion of the antifungal treatment and at 4 weeks and 6 months after treatment commenced. To assess compliance to the protocol and to record side effects, patients completed a questionnaire following treatment. Differences in the effects of the two formulations of itraconazole and any effects through time were analyzed by repeated-measures analysis of variance.

Nine male and 31 female patients whose ages ranged from 29 to 81 years (mean, 62 years) entered the study. Eighteen patients in each group completed the course of itraconazole and were evaluated. There was a general reduction in erythema with both forms of itraconazole. Patients in the cyclodextrin liquid group had a higher mean level of erythema at baseline than those in the capsule group, and incorporation of the baseline erythema meter index as a covariate in the repeated-measures analysis eliminated any significant treatment difference ($P = 0.38$).

The proportion of patients who removed their dentures for sleeping improved from 25% at baseline to 70% 6 months after treatment commenced. However, analysis of clinical visual denture cleanliness scores recorded throughout the study revealed little overall change between the initial and subsequent visits.

Eight patients (three receiving cyclodextrin and five who were administered capsules) were iron deficient (serum ferritin, <25 ng/ml) at baseline, and 12 (four in the cyclodextrin group and eight in the capsule group) had hyperglycemia (random blood glucose level, >6.0 mmol/liter) at the time of enrollment. Despite this, all demonstrated reduced erythema and yeast counts after antifungal treatment. There were no significant changes in hematologic indices, liver function test results, urea and electrolyte measurements, or C-reactive protein levels throughout the trial.

A wide range of yeast species were isolated from the mouths of the denture stomatitis patients before treatment (Table 1). Following antifungal therapy, patients were classified as having responded to treatment if they were mycologically cured or if the yeast count was reduced. The mycological response to treatment in each patient group is shown in Table 2. None of these results indicates any significant difference between the efficacies of the two preparations of itraconazole. Denture cleanliness in both treatment groups improved very slightly, but significantly ($P = 0.01$), by an average value of 0.3 (95% confidence interval, 0.1 to 0.5).

Completed questionnaires from 18 patients in each treatment group who had the entire course of itraconazole were available. In general, patients found their particular formulation of itraconazole pleasant and convenient to take. However, 12 patients in the cyclodextrin liquid group complained of gastrointestinal side effects such as diarrhea and stomach cramps. None of the patients who were administered itraconazole capsules reported any side effects. Subjectively, 15 of the patients on the liquid preparation and 9 of those taking capsules said that their mouths felt more comfortable following the course of antimycotic treatment.

Denture stomatitis is a multifactorial disease (6). Although treatment should be directed primarily toward reducing levels of denture plaque (1), most patients do not follow denture hygiene advice, as seen in this clinical trial. Overall, the results

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TABLE 1. The species of yeast isolated from patients with denture stomatitis before treatment

Study group	No. of isolates of species:						
	C. albicans	*C. glabrata*	*C. tropicalis*	*C. krusei*	*C. parapsilosis*	*Saccharomyces cerevisiae*	*C. guillermondii*
Cyclodextrin	20	5	1	0	0	0	0
Capsules	20	7	0	1	1	3	1
Total	40	12	1	1	1	3	1

of this study show that administration of an antifungal medication as an adjunct to other measures is significantly beneficial. Antifungal treatment should also be considered for patients who have other risk factors, such as diabetes mellitus, since beneficial effects were evident for 12 such patients in this study.

The two groups in the present investigation were well matched for age and sex, though there was an overall predominance of females, as might be expected because of the epidemiology of this condition (6). However, there was no difference between the sexes with regard to compliance with the two antifungal agent protocols or denture hygiene advice.

Itraconazole is clearly a very effective drug for use in the treatment of denture stomatitis. Both forms of itraconazole produced similar mycological responses, with 17 patients in the cyclodextrin liquid group and 18 in the capsule group being mycologically cured or having reduced yeast counts at the end of each treatment course. Although one patient in the cyclodextrin group had no change in yeast count on completion of the antifungal therapy, all patients in each treatment group had improved clinically by this stage in the trial, and it could be concluded that both preparations of itraconazole reduced the inflammation associated with denture stomatitis.

Some workers have reported that although fluconazole has a relatively narrow spectrum of activity (14), itraconazole shows a high potency against all of the commonly encountered pathogenic *Candida* species (10, 12, 16–18). Other studies, however, have indicated that neither fluconazole nor itraconazole is active against *Candida glabrata*, *Candida krusei*, or *Fusarium* species (11, 15). In all but three cases, when *C. glabrata* was one of the yeasts isolated at baseline in the present study, it persisted after antimycotic therapy.

Progressive recolonization of the mucosa and the denture-fitting surface by yeasts and the consequent recurrence of denture stomatitis after completion of antifungal treatment have been reported (2, 3, 8). In the present study, eight patients (22%) were free of yeasts at the 6-month review appointment. However, 50% of the patients who were mycologically cured at 2 or 4 weeks after treatment commenced were found to be recolonized by yeasts at 6 months.

TABLE 2. The mycological response to treatment in each patient group

Treatment group	Visit no.	*n*	No. of patients exhibiting the following mycological response:			
			Cure	Reduced yeast count	Increased yeast count	No change in yeast count
Cyclodextrin liquid	2	18	10	7	0	1
	3	18	11	4	3	0
	4	18	4	8	6	0
Capsule	2	18	7	11	0	0
	3	17	6	8	3	0
	4	17	8	7	2	0

The relationship between denture cleanliness and inflammation in denture stomatitis is well established (19). Although 70% of the patients followed the advice to remove their dentures at night, denture cleanliness did not improve substantially, as evidenced by both the clinical and the microbiological scores. This suggests that educating patients to improve their denture hygiene without providing adjunctive antifungal therapy is an unrealistic form of denture stomatitis treatment.

The triazoles are generally well tolerated (11, 14, 16). Routine hematological and biochemical investigations indicated no significant changes attributable to the itraconazole in this study. The two forms of itraconazole were similar with regard to ease of use and patient compliance, with only two patients from each treatment group failing to complete the 2-week course. However, an important difference between the two forms of itraconazole was seen in the incidence of gastrointestinal side effects. Two-thirds of the patients using the cyclodextrin liquid preparation complained of diarrhea, stomach cramps, or nausea during the course of itraconazole treatment. These symptoms were transient, resolved on completion of the course of itraconazole, and did not result in failure to complete the study. No gastrointestinal side effects were experienced by those taking capsules. Therefore, since the clinical and mycological responses to treatment were similar for the two preparations, the itraconazole capsules would be preferred over the cyclodextrin solution of itraconazole for outpatient management of denture stomatitis.

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