the Journal of CONTEMPORARY DENTAL PRACTICE at www.thejcdp.com

Comparative Evaluation of Ketoconazole Tablet and Topical Ketoconazole 2% in Orabase in Treatment of Candida-Infected Denture Stomatitis

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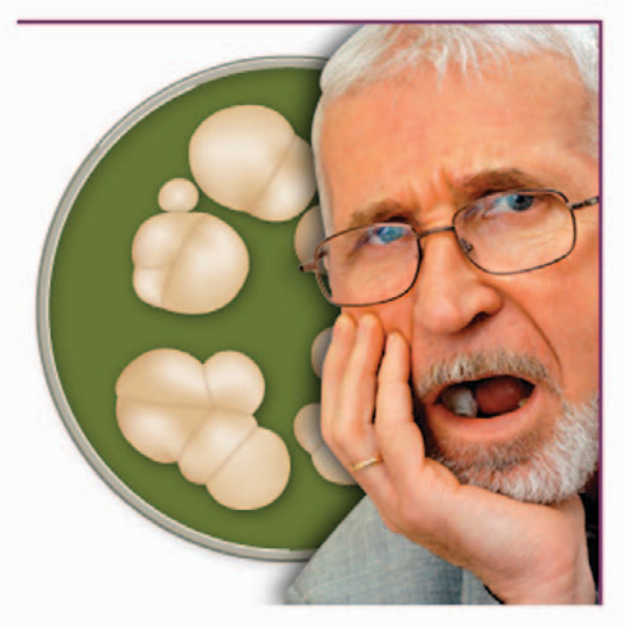
Abstract

Aim: Denture stomatitis is a common and recurring problem of denture wearers. Ketoconazole tablet is one of the antimycotic drugs that often has been used to treat this condition, but systemic use of this drug has some adverse effects that frequently lead to unfavorable compliance and treatment failure. This study was designed to compare the efficacy of topical ketoconazole 2% in orabase and ketoconazole tablet.

Methods and Materials: Thirty patients with denture stomatitis (positive culture) were divided into two groups. The first group received ketoconazole tablet (orally used 200 mg per day) for 14 days and the second group received 2% topical ketoconazole in orabase applied twice daily on the mucosal denture surface. Candida cultures were taken from the palatal mucosa before and on days 7 and 14 after commencement of the therapy. The mean of colonies before and 7 and 14 days after medication were calculated. One-way ANOVA and paired t-test were used for data analysis (α=0.05).

Results: The mean of colonies number before receiving medication in the tablet and topical application groups were 454 and 441 respectively. The mean of colonies number after receiving medication in tablet and topical application group were 137 and 176 (on the seventh day) and 122 and 96 (on the 14th day), respectively; there was no significant difference between the two groups after medication (p=0.18).



Conclusion: Topical ketoconazole 2% in orabase can be useful in managing denture stomatitis. This topical medication has fewer side effects, whereas systemic administration of ketoconazole tablet is associated with some complications.

Clinical Significance: The application of topical ketoconazole 2% in orabase ointment can be considered in the treatment of denture stomatitis and has comparable efficacy with the ketoconazole tablet.

Keywords: ketoconazole, orabase, candida, denture stomatitis, topical treatment.

Citation: Khozeimeh F, Shahtalebi MA, Noori M, Savabi O. Comparative Evaluation of Ketoconazole Tablet and Topical Ketoconazole 2% in Orabase in Treatment of Candida-infected Denture Stomatitis. J Contemp Dent Pract [Internet]. 2010 March; 11(2):017-024. Available from: http://www.thejcdp.com/journal/view/volume11-issue2-khozeimeh.

Introduction

Denture stomatitis is a common form of chronic oral candidiasis that manifests as a diffuse inflammation of the maxillary denture-bearing areas.[1] In selected populations the prevalence of denture stomatitis has been found to vary from 10% up to 65%.[2–5] At least 70% of the individuals with clinical signs of denture stomatitis exhibit fungal growth and this condition most likely results from yeast colonization.[6] *Candida* specimens act as an endogenous infecting agent on tissue predisposed by chronic trauma to microbial invasion.[1] Decreased salivary flow rate, medication, various endocrinopathies, nutritional and metabolic factors,[7] and defects in the host defense mechanism[8] are among the systemic predisposing factors. Local predisposing factors suggest poor denture hygiene, retention, and stability.[9] The mucosa beneath the denture becomes red, swollen, smooth or granular and is sometimes painful.[9] Multiple pinpoint foci hyperemia usually involving the palate frequently occurs. A severe burning sensation is not uncommon.[9] The redness of the mucosa may be sharply outlined and restricted to tissue in contact with the denture. Fungi, mostly *Candida albicans*, are usually the infectious agent in denture stomatitis.[9] *Candida* infection had been considered an important factor in the pathology of denture stomatitis.[10,11] The unique microenvironment provided by a denture may promote *Candida albicans* to proliferate without any other predisposing factors present. As *Candida albicans* accumulates in its pathogenic form, hyphae, an intense immunologic reaction, is seen and denture stomatitis develops.[12] Treatment should start with meticulous denture hygiene and removing or reducing other local and systemic predisposing factors, for example, ill-fitting dentures, sufficient nutritional intake, or antibiotics and medication causing hyposalivation.[9]

If the symptoms do not disappear, infection should be controlled by antimycotic drugs.[9] Elder patients with predisposing factors such as xerostomia and immunodeficiency may need long-term use of several antimycotic drugs, which can lead to developing several side effects that frequently cause unfavorable compliance and treatment failure.[1]

Some topically administered antifungal drugs have been used and compared with systemic applications in the treatment of denture stomatitis in several studies.[9,13–17]

The efficacy of a topically administered miconazole denture lacquer was compared with that of a placebo lacquer in the treatment of *Candida*-infected denture stomatitis. The results indicate that a single application of a miconazole denture lacquer considerably reduces the number of *Candida* yeasts for a substantial period of time.[9]

In another study, commercially available miconazole 2% gel applied four times daily for two weeks was statistically more efficient than the miconazole lacquer applied once on the denture tissue surface.[13] As well miconazole 2% gel reduces the colony count of the denture surface more efficiently than *Zataria multiflora* 0.1 gel applied four times daily for two weeks.[14] The comparison of fluconazole capsules and hexetidine mouthrinses for the management of denture stomatitis detected no statistically significant difference in *Candida albicans* counts in saliva,

lesion, and denture after treatment between two groups.[15] And finally, it has been shown that fenticonazole, nystatin, and ketoconazole 2% in orabase in the topical treatment of oral chronic candidosis can significantly decrease the oral lesions.[16]

The aim of this study was to compare the efficacy of topically administered ketoconazole 2% in orabase with a once-daily dose of a 200 mg ketoconazole tablet for treatment of *Candida*-associated denture stomatitis.

Methods and Materials

Complete denture wearers between 56 and 90 years old were selected from a geriatric sanatorium in Isfahan. All the individuals had moderate to severe erythematous palatal mucosa and received no antibiotics, antimycotics, or any drug that caused hyposalivation within one month before the study. Sterile swabs were taken from each individual's palatal mucosa and were cultured on a dextrose sabouraud agar plus chloramphenicole plate and incubated for 48 hours at 37°C. The individuals with less than 100 colonies of candida were excluded from the study. Finally 30 patients were selected for a randomized clinical trial and divided into two groups. One group received one daily dose of a 200 mg ketoconazole tablet and the other group received topical ketoconazole 2% in orabase ointment that was prepared by the pharmaceutical research laboratory at the School of Pharmacy, Isfahan University of Medical Sciences in Isfahan, Iran.

Individuals were instructed to apply a fine layer of topical ointment with a fine brush on the palatal mucosa twice a day, in the morning after breakfast and at night before sleeping. The same culturing procedure explained above for inclusion criteria was used for individuals 7 and 14 days after treatment. The study was approved by the Committee of Ethics and Research of the School of Dentistry of Isfahan University of Medical sciences. (# 384034)

One-way analysis of variance and paired t-test were used for data analysis (α=0.05).

Results

At inclusion, the mean number of colonies in the tablet group was 454 and in the ointment group, 441 (Table 1). No statistical difference was found between the two patient groups related to culture results (p=0.18).

Seven days after application of the ointment, the mean number of colonies in this group was 176; in the tablet group it was 137.

Fourteen days after application, the mean number of colonies in the ointment group was 96; in the tablet group it was 122.

In the ointment group the differences between the days 0 and 7 (p=0.018), 0 and 14 (p=0.006), and 7 and 14 (p=0.029) were statistically significant, while in the tablet group the differences between days 0 and 7 (p=0.013) and 0 and 14 (p=0.011) were statistically significant, but no statistically significant difference was found between days 7 and 14 (p=0.723).

Table 1. Mean number of colonies before and after treatment in two groups.

Group	Mean number of colonies Day 0	Mean number of colonies Day 7	Mean number of colonies Day 14
Tablet	454	137	122
Std. error of mean	115.429	32.805	34.522
Ointment	441	176	96
Std. error of mean	135.170	50.831	32.804

Discussion

A variety of topical and systemically administered medications are now available to supplement the older polyene antifungal antibiotics, nystatin and amphotericin B, for treatment of oral candidiasis.[1]

One imidazole derivative that is effective in treatment of both acute and chronic candidiasis is ketoconazole tablet, which is usually administered by use of a once-daily dose 200 mg tablet in systemic therapy, but when this medication is used for a long period, (as in the treatment of the chronic form of candidiasis) side effects may occur.[1] These side effects included gastrointestinal disturbances, nausea, vomiting, diarrhea, constipation, abdominal pain, transient elevation in the serum concentration of liver enzymes, hepatitis, gynecomastia, adrenal cortex suppression, hypersensitivity reactions, pruritus, rash, headache, dizziness, and somnolence. Also rarely ketoconazole has been associated with severe depression, hair loss, thrombocytopenia, paraesthesia, and photophobia.[18] On the other hand, topical ketoconazole was first approved as a cream formulation in 1985 and a shampoo in 1990. It has no significant side effects.[19] The most commonly reported side effects included irritation, pruritus, and stinging.[18]

Table 1 shows the mean number of colonies in the tablet group and the ointment group on days 0, 7, and 14. After 14 days of treatment, the mean number of colonies decreased significantly in the two groups ($p<0.001$).

Although the reduction in the mean number of colonies in the ointment group was greater than in the tablet group, the statistical difference was not significant ($p=0.999$).

However, it would have been preferable to follow the effect of a topical application for a longer period of time, for example, for five to six weeks.

Comparative efficacy of the topical slow-release mucoadhesive miconazole nitrate versus systemic therapy with ketoconazole in HIV-positive patients with oropharyngeal candidiasis indicates that the low dose (10 mg) of the miconazole mucoadhesive tablet is not inferior to the systemic antifungal treatment with ketoconazole, whereas a higher incidence of gastrointestinal disorders and drug-related adverse events were seen during ketoconazole treatment.[20] Also miconazole 50 mg mucoadhesive buccal tablets were well tolerated and thus may be recommended as first-line treatment in cancer patients who have oropharyngeal candidiasis as an alternative to systemic agents.[21]

Figure 1 illustrates the difference in colonies between the two groups on days 0, 7, and 14. Figure 1 further illustrates the less effectiveness of the treatment in the second week as compared to the first week in both groups, although the

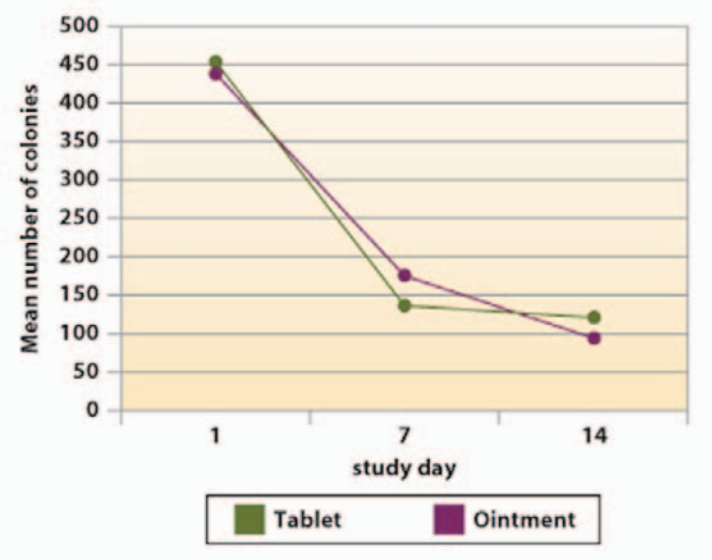


Figure 1. Mean number of colonies during the study period (days 0–14) in two groups.

differences between day 7 and day 14 in the ointment group were statistically significant (p=0.029).

This effect is probably due to two factors:

1. Development of relative resistance to ketoconazole, especially in the tablet group. In 1996 Silverman[22] observed that 81% of the cultures remained positive after antifungal oral treatment with ketoconazole orally for seven days. On the other hand, approximately one-half of the patients treated by Graybill[23] relapsed one month after completion of treatment. Silverman[22] suggests that much of what is regarded as resistance may represent inadequate dosage or time of treatment or both.
2. The presence of several predisposing factors such as xerostomia, immunodeficiency, and insufficient nutritional intake that cannot be eliminated; we know that these predisposing factors are very important in the etiology, persistence, and recurrences of this infection.

Also adhesion and enzyme production in *Candida albicans* could be factors that, along with predisposing conditions related to the host, determine if an individual will develop the disease or remain as a healthy carrier.[24]

However these patients, especially if underlying predisposing factors cannot be eliminated, may need either continuous or repeated treatment, improved denture hygiene, and improved nutritional status.

In summary the application of topical ketoconazole 2% in orabase ointment proved effective in reducing the number of *Candida* colonies in cultures taken from the palatal mucosa of geriatric patients with denture stomatitis and has minimal side effects in long-term administration, compared with a ketoconazole tablet in systemic use. In such patients a clinically effective antifungal agent that yields high patient compliance would be an advantage over more conventional antifungal agents.

Conclusion

1. Ketoconazole tablet and ketoconazole 2% in orabase were of comparable efficacy in the treatment of denture stomatitis according to culture results.
2. In the ointment group the differences in the mean number of colonies between days 7 and 14 was statistically significant, while in the tablet group no statistically significant difference was found between days 7 and 14.
3. Clinicians may consider topical ketoconazole as an alternative with fewer side effects than oral ketoconazole.

Clinical Significance

The application of topical ketoconazole 2% in orabase ointment can be considered in the treatment of denture stomatitis and has comparable efficacy with the ketoconazole tablet.

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Acknowledgement

This study was supported by Isfahan University of Medical Sciences Research Grant #384034. Based on the thesis submitted to the school of dentistry for partial fulfillment of the requirement of the DDS degree.