Fluconazole versus nystatin in the treatment of oral candidosis

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The efficacy of oral fluconazole versus nystatin was evaluated as a treatment modality for oral candidosis. Of the included patients ($n = 60$), two-thirds presented with an erythematous candidosis, and the others showed clinical signs compatible with a pseudomembranous candidosis. Predisposing factors were xerostomia ($n = 18$), HIV ($n = 5$), immunosuppression in conjunction with organ transplantation ($n = 10$), and wearing of dentures ($n = 14$). For the remaining patients no specific predisposing factors were found. One patient who was treated with nystatin was excluded owing to nausea that was related to the antifungal treatment. After 7 days of treatment with fluconazole (50 mg/day), the affected oral mucosa, assessed by the investigator, was cured or showed considerable improvement in 87% of the patients ($n = 30$). The corresponding figure for the nystatin group ($n = 30$), rinsing with 1 mL 4 times a day for 21 days, was 80%. Following treatment with fluconazole, 20 of 22 patients with symptoms at the start (91%) reported improvement. The comparable figures for the nystatin group were 10 of 12 patients (83%). Half of the patients in the nystatin group reported inconvenience from taking the medication (mean value = 25.9) compared with 23% of the patients in the fluconazole group (mean value = 6.6). Eight patients in the fluconazole group and 12 patients in the nystatin group exhibited a relapse within 6 months. These differences were not found to be statistically significant. The patients in the fluconazole group reported less inconvenience from taking the medication, a finding that may have clinical implications for compliance. □ *Antifungal agents; antifungal antibiotics; drugs; immunosuppression; opportunistic infection*

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Different species of *Candida* are considered to be a part of the normal oral flora in approximately 40% of the total population (1). With this high prevalence figure it is not surprising that opportunistic oral candidosis frequently develops as a sequel to local and systemic immunosuppression. Several predisposing factors have been identified, including wearing of dentures, dietary factors, disturbed oral ecology, xerostomia, heavy smoking, insufficient oral hygiene, and immunosuppressive medication and disorders (2). Elimination of these factors is sometimes possible to accomplish, resulting in eradication of the infection, but persisting fungal infections may occur that justify the use of antifungal agents.

Currently, topical agents such as nystatin are widely used in the treatment of oral candidosis. Nystatin is administrated as a mixture and requires multiple applications each day. Although the taste of nystatin may cause nausea, the number of patients who report adverse effects of the medication is very low (3, 4).

Fluconazole is a water-soluble triazole that has been reported to be highly effective in the treatment of oral candidosis (5–8). This antimycotic agent is administered as a capsule once a day. Concomitant with its widespread use, concerns have been raised regarding the development of resistance in long-term treatment of oropharyngeal candidosis in AIDS patients. However, no such adverse effect seems to appear following short courses of therapy.

The aim of this single-blind study was to assess which of the two treatment strategies, systemic fluconazole or topical nystatin, is the most efficient to use in the treatment of oral candidosis. The study was focused on clinical signs, symptoms, adverse effects, relapses, and attitudes toward the use of the agents.

Materials and methods

Seventy-one patients with the tentative diagnosis of oral candidosis were consecutively selected from patients referred to two oral medicine clinics in Göteborg. The study was approved by the local ethics committee, and informed consent was obtained from all patients. At the primary examination a standardized form was used to register demographic data and complete medical history, including current medication. The clinical appearance of the oral infection was documented by photographs. The subjective complaints were measured with a visual analog scale (VAS). For the VAS measurement the patients were exposed to a measuring stick with a 10-cm line, marked with 'no discomfort' on the left and 'worst imaginable discomfort' on the right. The patients were asked to mark on the line according to the actual sensation of discomfort related to their oral infection. All patients presented clinically with at least one of the types of oral candidosis according to the recent classification by Holmstrup & Axéll (9). Patients were excluded from the study if they had

Table 1. Predisposing factors, type of candidosis, and demographic data

Predisposing factor	No. of patients	Men	Women	Mean age (years)	Erythematous candidosis	Pseudomembranous candidosis	VAS start*
Fluconazole							
Xerostomia	9	3	6	50	7	2	51 ($n = 8$)
HIV	2	2	0	36	1	1	20 ($n = 2$)
Immunosuppression	5	1	4	59	3	2	21 ($n = 4$)
Dentures	7	3	4	64	7	0	49 ($n = 3$)
Not found	7	3	4	70	3	4	44 ($n = 5$)
Total	30	12	18	58.4	21	9	41 ($n = 22$)
Nystatin							
Xerostomia	9	3	6	68	3	6	44 ($n = 3$)
HIV	3	3	0	45	2	1	50 ($n = 1$)
Immunosuppression	5	1	4	52	3	2	53 ($n = 3$)
Dentures	7	4	3	64	7	0	52 ($n = 2$)
Not found	6	3	3	52	5	1	37 ($n = 3$)
Total	30	14	16	60.7	20	10	47 ($n = 12$)

* Mean value of the VAS score at the primary examination; number of patients with symptoms in parentheses.

received any antifungal treatment in the last month. The clinical diagnosis had to be verified by microbiologic analysis. Following microbiologic sampling with a slight curettage of the mucosa, smears were transferred to glass slides for direct microscopy. Samples were also transferred to test tubes containing a transport medium (VMGIII, Department of Oral Microbiology, Göteborg University, Sweden). These samples were immediately transported to the microbiologic laboratory, where they were cultured on Sabouraud-Dextrose-agar (Difco, Detroit, Mich., USA) containing 0.01% tetrasodium chloride.

At the end of the primary examination, the patients were assigned to receive either fluconazole or nystatin. The first patient in each group was randomly selected to receive one of the two medicaments by a study coordinator who was not involved in patient care. The following patients were then alternately assigned to fluconazole or nystatin treatment. An attempt at conventional stratification gave a distorted distribution, and therefore the method of alternate assignment was used. As a number of dentists from two different clinics were involved in the study, it was impossible for them to unveil what medicament was in turn to be used. The assignment was done blinded to the clinical investigators by dental assistants who also gave the instructions of the study procedures to each patient. Patients treated with nystatin solution ($n = 35$) were instructed to use 1 mL of the solution for rinsing for 5 min. The patients were informed not to swallow the mixture following rinsing. The treatment was repeated 4 times daily for 3 weeks. Patients treated with fluconazole ($n = 36$) received capsules (50 mg) and were instructed to swallow 1 capsule each day for 7 days.

In 3 patients in the fluconazole group and 1 patient in the nystatin group, the microbiologic cultivation did not verify the clinical diagnosis, and these patients were excluded from the study. Of the remaining 67 patients, 33 had randomly been assigned at the primary examination to the fluconazole group and 34 to the nystatin group.

The patients were followed up 7 and 21 days after the primary examination, and thereafter once a month for 6 months. Clinical data at day 7 were used to evaluate the treatment efficacy for the fluconazole group, and at day 21 for the nystatin group. If a relapse of oral candidosis was revealed after 21 days or at one of the later follow-ups, the study of that patient was terminated. At the first follow-up the patients had to assess their complaints by the use of a VAS and were also asked about their experience of using the medication. This was measured by the use of a VAS as well. A clinical examination was also performed, and photographs from the primary examination were compared with the clinical appearance at the follow-ups. On both occasions the clinical results were scored as cured, improved, or failure. The term 'cured' was used when the oral mucosa was healthy and free of clinical signs of candidosis. The oral mucosa was classified as 'improved' when a reduction in size of the infection was observed in comparison with the situation at the primary examination. 'Failure' was used to denote an oral mucosa with unchanged clinical characteristics of oral candidosis following treatment. Clinical photos were used to assist in the clinical evaluation of the treatment results.

Statistical analysis

Chi-square analysis, Student's t test, and the Mann–Whitney U-test for independent samples were used to test for significant differences.

Results

Premature discontinuation of fluconazole or nystatin treatment was required in seven patients. Discontinuation for medical reasons ($n = 4$) included deteriorated health conditions, fatigue, and termination of the medication by other nursing staff. One patient in each group died during

Table 2. Clinical scoring of treatment effects

	Cured	Improved	Failure
Fluconazole	9	17	4
Nystatin	5	19	6

the course of the trial; neither death was related to the antifungal medication.

Side effects were reported by one patient only. This patient was treated with nystatin and discontinued treatment because of nausea. The remaining patients, 30 in the fluconazole group and 30 in the nystatin group, were considered evaluable for efficacy, and data of the included patients are presented in Table 1. Patients reporting dryness of the mouth were assigned to the xerostomia group. Organ-transplanted patients who received immunosuppressive drugs were included in the group 'Immunosuppression', and patients wearing dentures in the upper jaw were assigned to the 'Denture' group.

Although differences in the clinical response (Table 2) between the two antifungal agents were revealed, these findings were not statistically significant. Eight patients in the fluconazole group and 12 patients in the nystatin group exhibited a relapse within 6 months. These differences were not found to be statistically significant. Immunosuppressed patients, who improved and returned to a normal immune function during the course of the study, had fewer relapses than patients who continued to have a predisposing factor for candida infection. However, the numbers in these groups were small, and a statistical analysis was not meaningful.

The numbers of patients with subjective symptoms related to oral candidosis at the start in the two groups differed considerably (fluconazole group: $n = 22$, mean VAS = 41.1, standard deviation (s) = 22.1; nystatin group: $n = 12$, mean VAS = 46.6, $s = 20.4$), but the mean VAS values were virtually identical. These data indicate that the symptomatic patients in the two groups did not present with any significant difference regarding the severity of their oral candidosis.

As demonstrated by the figures in Table 3, no statistically significant difference between the two groups was revealed when mean differences in VAS figures for those patients who reported an improvement were compared. VAS difference was calculated as the difference between the VAS value at the start and the value reported by these patients at the first follow-up. At the follow-up appointment 16 patients in the fluconazole group (mean VAS = 21.4, $s = 18.1$) and 13 patients in the nystatin group (mean VAS = 26.5, $s = 19.0$) complained of oral discomfort. In the latter group 4 patients who were non-symptomatic at the start reported symptoms following treatment. None of the non-symptomatic patients in the fluconazole group reported the same experience. Fifteen of 22 patients in the fluconazole group and 7 of 12 patients in the nystatin group reported a reduction in VAS value exceeding 50%. No statistically significant differences were observed when comparing the numbers of patients who reported a total relief of symptoms in the two treatment groups (fluconazole group, 6 of 22; nystatin group, 3 of 12).

The patients in the fluconazole group reported less inconvenience related to the use of the antifungal medicament than the group treated with nystatin (Table 3). In the former group 7 patients complained about taking fluconazole, revealed by VAS values from 1 to 15. In the nystatin group 15 patients reported some discomfort related the antifungal agent, and the VAS values ranged from 1 to 100.

Discussion

Candida is a benign commensal organism frequently encountered in healthy people. This microorganism is typically opportunistic and lacks the pathogenic features necessary to instigate a fungal infection. Thus, local or general predisposing factors are required for candida to establish an infection. Accordingly, management of candida infections should always be directed toward eradicating these predisposing factors, but when this is not possible to achieve, antifungal agents are warranted.

Cessation of the antifungal treatment without a simultaneous elimination of the predisposing factor will frequently be followed by a relapse of the infection (5, 6).

Table 3. Number of patients with symptoms at start who reported an improvement (+), no effect (0), or failure (−) following treatment, and number of patients who reported an inconvenience from taking medication

	Self-reported treatment effects					Self-reported inconvenience from taking medication		
		VAS difference*					VAS score*†	
	+	Mean	s	0	−	n	Mean	s
Fluconazole	20	28.4	19.1	1	1	7	6.6	4.8
Nystatin	10	34.4	17.1	0	2	15	25.9	28.0

* Mean values and standard deviations (s) of self-reported VAS differences are given for the patients who reported an improvement related to treatment efficacy and for VAS figures reflecting inconvenience from taking the medication.
† Chi-square = 4.59, $P = 0.032$; Mann–Whitney U-test = 15.0, $P = 0.008$.

This was observed in the present study, in which the infection relapsed in one-half to one-third of the patients. The reason for instant relapses is most likely that predisposing factors have not been eliminated. This suggestion was supported by the observation that immunosuppressed patients who gained a normal immune function during the course of the study were more likely to get a permanent cure than patients for whom the predisposing factors were not successfully eliminated.

It has been reported that virtually no alterations in the histopathologic reaction pattern are observed following treatment of denture stomatitis with topical antifungal agents (10). Thus, persisting inflammation may also contribute to relapses of oral candidosis. Longer treatment periods than used in the present study may promote total healing of inflammation and prevention of immediate relapse of the candida infection.

No statistical difference in the outcome of treatment was revealed between the two groups as assessed by clinical scoring. Approximately 80% of the patients in both groups were cured or showed an improvement. These results were not found to follow the improvement self-reported by the patients in the two groups. It should be emphasized that clinical scoring was carried out using a scoring system with three different levels, while the self-reported assessment was performed with a more continuous scale. Most likely, the VAS instrument was able to identify more subtle differences than the clinical scoring system. Another explanation of the difference between self-reported data and clinical observations may be that improvement of the candida infection is first revealed by a decline in symptoms followed by a disappearance of clinical features of inflammation.

Compared with the patients in the nystatin group, those in the fluconazole group felt it easier to take the antifungal agent. This may have implications for compliance, particularly in patient groups for whom rinsing with a topical medicament four times a day is difficult for reasons such as delicate health and interference with other activities.

In patients suffering from general immunodeficiencies, systemic antifungal treatment is recommended as, most likely, other locations in the body are infected or predisposed to be infected. A topical antifungal agent will be effective only at the site of application, and systemic effects are not likely to occur. The use of antifungal agents as part of a prophylactic strategy in case of systemic immunodeficiency should also be confined to systemic agents, as use of topical antifungal agents may mask development of a candida infection that may appear in other parts of the body. However, the use of topical antifungal agents is justified in case of symptoms caused by a candida infection that is a sequel to a local predisposing factor such as hyposalivation or local steroid treatment. It should be emphasized that an attempt to eliminate predisposing factors should always be conducted prior to the use of antifungal medication.

From the present study it can be concluded that both fluconazole and nystatin have low side effects and are well tolerated. No differences between the two antifungal agents were found regarding clinical effects or the symptoms described by the patients.

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