Oropharyngeal Candidiasis in Patients with AIDS: Randomized Comparison of Fluconazole Versus Nystatin Oral Suspensions

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A total of 167 human immunodeficiency virus (HIV)–infected patients with oropharyngeal candidiasis were randomly assigned to receive 14 days of therapy with liquid suspension fluconazole (100 mg once daily) or liquid nystatin (500,000 U four times daily). At day 14, 87% of the fluconazole-treated patients were clinically cured, as opposed to 52% in the nystatin-treated group (P < .001). Fluconazole eradicated Candida organisms from the oral flora in 60%, vs. a 6% eradication rate with nystatin (P < .001). The fluconazole group had fewer relapses noted on day 28 (18%, vs. 44% in the nystatin group; P < .001). This relapse difference no longer existed by day 42. Fluconazole oral suspension as a systemic therapy was more effective than liquid nystatin as a topical therapy in the treatment of oral candidiasis in HIV-infected patients and provided a longer disease-free interval before relapse.

In the 1980s, the rates of oropharyngeal candidiasis (oral thrush) increased >4-fold, and those of disseminated candidiasis increased >10-fold [1]. Oropharyngeal and esophageal candidiasis are the most frequently diagnosed opportunistic infections in the immunocompromised host [2–4]. Oral candidiasis occurs in >90% of patients with AIDS at some time during their illness [5]. These infections can be severe, are usually recurrent, are a marker of the severity of immunosuppression [6], and are linked to the progression of AIDS [7]. The presence of thrush in the absence of predisposing factors may be the first clue to the diagnosis of HIV infection. A burning sensation, local pain and discomfort, and loss of taste are common symptoms of this infection.

Oral candidiasis has been treated most often with topical agents such as nystatin and clotrimazole, but few comparative clinical trials have been performed. In a previous study we found no significant differences between the efficacy of oral fluconazole tablets and clotrimazole troches, both of which were highly effective in treating oral candidiasis [8]. This randomized prospective multicenter study was designed to evaluate and compare the efficacy and toxicity of oral liquid fluconazole suspension, given once daily, with those of liquid nystatin, given four times daily as a swish-retain-swallow regimen, in the treatment of oral candidiasis in HIV-infected patients.

Patients and Methods

A total of 167 patients were enrolled in the study. Eligible patients (1) met the criteria of the Centers for Disease Control and Prevention for a diagnosis of AIDS or had serological evidence of HIV infection and (2) had typical signs and symptoms of oropharyngeal candidiasis. Diagnosis was confirmed in all cases by the presence of typical pseudohyphae or hyphae forms, which were identified in a swab or scraping specimen from an oral lesion or area of erythema; identifications were confirmed by mycologic culture. Patients with signs or symptoms of esophagitis were excluded from the study unless esophagoscopy results were negative. Informed consent was obtained from all participants.

Patients who were taking other forms of antifungal therapy at or within 3 days of enrollment (baseline) were excluded, as were patients who had a known history of intolerance to imidazoles, triazoles, or the polyene components of nystatin. Patients who concomitantly received phenytoin, oral hypoglycemic therapy, coumarin-type anticoagulants, and cyclosporine were allowed to participate but required ongoing monitoring during the study.

Additional exclusion criteria included an inability to tolerate oral medications, the presence of moderate or severe liver disease (i.e., an aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase level >3 times the upper limit of normal; a bilirubin level of >3 mg/dL; or a partial thromboplastin time of >5 seconds over the control value and not correctable by vitamin K administration), life expectancy of <4 weeks, and an inability to be followed at one center for the study duration.

Baseline evaluations included determination of the medical history and physical examination. Signs and symptoms of oropharyngeal candidiasis were recorded. Baseline laboratory as-
sessments (determination of the complete blood cell count and levels of platelets, aspartate aminotransferase, alanine aminotransferase, bilirubin, serum creatinine, blood urea nitrogen, and alkaline phosphatase) were performed. Within 48 hours of enrollment, swab or scraping specimens of lesions in clinically involved oral mucosa were examined for the presence of pseudohyphae or hyphae, and specimens were cultured for Candida species. Patients with obvious clinical disease whose microscopy results were positive were allowed to begin therapy while culture results were awaited. Those whose cultures were negative were deemed inevaluable and eliminated from the study.

Eligible patients were randomly assigned to receive either fluconazole oral suspension or nystatin oral suspension for 14 days. Patients receiving fluconazole took 100 mg (10 mL) once daily for 14 days (with a 200-mg [20-mL] loading dose on day 1), and patients receiving nystatin took 5 mL (500,000 U) four times daily for a total of 14 days. Patients receiving fluconazole were instructed to swallow the suspension directly, at approximately the same time every day. Nystatin recipients were directed to swish and then retain each dose in the mouth for as long as possible before swallowing, as prescribed in the package insert for this drug.

Six evaluations took place during this study, on days 1, 3, 7, and 14 (end of treatment) and days 28 and 42 (follow-up). At each visit any signs and symptoms of oral candidiasis were noted. Oral sampling was repeated for microscopy and fungal culture on days 7 and 14. Swab and scraping specimens were obtained again on days 28 and 42 only if clinical lesions or erythema in the oropharynx reappeared. When no lesions were present, their absence was recorded. The clinical evaluator at each study point was unaware of what drug the patient was taking.

Efficacy Criteria

To be considered evaluable for primary clinical efficacy, patients had to have mycologically confirmed, symptomatic oropharyngeal candidiasis at baseline. They had to have received at least 5 days of therapy with fluconazole (five doses) or nystatin (20 doses). No other antifungal therapy was allowed during the study. End-of-treatment culture and/or microscopic examination was required for all participants.

Adverse events were assessed at each visit. Compliance with study protocol was assessed with use of drug administration records or by measuring the remaining suspension volume. Laboratory evaluations were repeated on days 7 and 14.

Clinical and Mycologic Assessment

Patients were assigned to response categories by the investigators at the end of treatment. Clinical cure was defined as the complete resolution of signs and symptoms of oropharyngeal candidiasis, and clinical improvement was defined as a decrease in lesions, erythema, and symptoms despite the continued presence of disease. When there was no change or the candidiasis progressed, the case was designated a treatment failure.

Mycologic cure or eradication was characterized by the absence of Candida species in cultures on day 14 (end of treatment). Colonization was defined by a Candida-positive culture in the absence of clinical disease. Mycologic failure was defined by a positive culture and the presence of clinical disease.

Patients in whom clinical resolution or improvement was noted on day 14 were seen for posttreatment follow-up on days 28 and 42. Patients who were clinically cured but had mycologic evidence of infection were also seen on the same follow-up schedule, but mycologic colonization was considered to have occurred because of the failure of the study treatment to eradicate the Candida organisms. For patients in whom clinical cure or improvement and mycologic cure were not achieved, treatment was designated as a failure, and these patients were withdrawn from the study.

Statistical Methodology

The primary study endpoint was clinical response to treatment, as expressed in the proportions of patients who were clinically cured in both groups (with use of the Mantel-Haenszel $\chi^2$ test adjusted for study site). Tests were two-tailed and based on a .05 level of significance. Frequencies of relapse on or before follow-up visits (days 28 and 42) were also compared.

Results

Of the 167 patients enrolled in the study, 83 were randomly assigned to receive fluconazole and 84 to receive nystatin. In both groups, the male:female ratio was 7:1 and the mean age was 38 years. The degree of severity of signs and symptoms of candidal infection at baseline for both treatment groups is shown in table 1. No statistically significant differences in clinical manifestations were evident between groups at baseline. Of the enrolled patients, 69 fluconazole and 69 nystatin recipients were evaluable for clinical outcome. Mycologic outcome was evaluable in 68 fluconazole-treated patients and 66 nystatin-treated patients.

Table 2 shows the clinical and mycologic outcome for the evaluable patients at the end of therapy and data on relapses noted on days 28 and 42. Twenty-nine patients (14 fluconazole and 15 nystatin recipients) discontinued participation in the study before day 14 and were not evaluated for efficacy: 16 were lost to follow-up (8 fluconazole and 8 nystatin recipients), treatment failed for 2 (1 fluconazole and 1 nystatin recipient), 6 committed protocol violations (2 fluconazole and 4 nystatin recipients), and 5 had adverse reactions and/or laboratory value abnormalities (3 fluconazole and 2 nystatin recipients).

Another 25 fluconazole-treated and 52 nystatin-treated patients were withdrawn after day 14 but before the end of the study, on account of relapse or reinfection (8 fluconazole and 34 nystatin recipients), loss to follow-up (3 fluconazole and 1 nystatin recipient), adverse reactions or laboratory value abnor-
Table 1. Signs and symptoms at baseline in 167 HIV-infected patients with oropharyngeal candidiasis who received treatment with oral fluconazole suspension or liquid nystatin.

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Baseline severity*</th>
<th>Fluconazole (n = 83)</th>
<th>Nystatin (n = 84)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>None</td>
<td>6.0</td>
<td>2.4</td>
<td>.283</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>20.5</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>59.0</td>
<td>60.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>14.5</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Oral discomfort³</td>
<td>None</td>
<td>2.4</td>
<td>1.2</td>
<td>.377</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>23.2</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>54.9</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>19.5</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Oral lesions³</td>
<td>None§</td>
<td>18.3</td>
<td>15.5</td>
<td>.608</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>40.2</td>
<td>38.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>37.8</td>
<td>45.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3.7</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

* Mild = <10% involvement; moderate = 10%–50% involvement; severe = >50% involvement.
† Mantel-Haenszel $\chi^2$ test.
³ n = 82 at baseline for oral discomfort and lesions.
§ Only erythema was present.

Clinical and Mycologic Response

A total of 60 (87%) of the 69 evaluable patients in the fluconazole group were considered clinically cured, as opposed to 36 (52%) of 69 evaluable patients in the nystatin group. There were 8 clinical improvements and 1 treatment failure in the fluconazole group and 11 improvements and 22 failures in the nystatin group (P < .001). Eradication of Candida species was achieved by the end of treatment (day 14) in 41 of 68 fluconazole-treated patients (60%) vs. 4 of 66 nystatin-treated patients (6%) (P < .001).

Relapses had occurred in both treatment arms by the time of the follow-up evaluations (days 28 and 42) (table 2). Although more patients remained disease-free in the fluconazole group at day 28, there were no statistically significant differences in relapse after day 28 between the two groups at the end of the follow-up (day 42). Candida albicans accounted for 95% (128) of the 134 Candida isolates in baseline cultures and 93% (83) of the 89 isolates representing colonization or failures.

Safety

Overall, both therapies were well tolerated. In both treatment groups, the most commonly reported adverse events were gastrointestinal (e.g., nausea, diarrhea, and vomiting). One fluconazole recipient withdrew from the study because of nausea, and one nystatin recipient withdrew because of vomiting. Elevated liver enzyme concentrations were documented in two fluconazole recipients and caused one patient to be withdrawn.

Discussion

The diagnosis of oral candidiasis can serve as a diagnostic marker of HIV infection and also as a signal of disease progression in patients known to be HIV seropositive, as evidenced by the relationship of this infection to decreasing CD4 lymphocyte counts [6]. This study sought to compare a new liquid dosing
formulation of fluconazole (once daily) with the standard topical therapeutic agent of liquid nystatin (four times daily) in the swish-retain-swallow regimen. The clinical cure rate of 87% and mycologic cure rate of 60% for fluconazole oral suspension are remarkably similar and consistent with previously published results concerning use of fluconazole tablets [8], a finding suggesting equal efficacy for these two formulations of fluconazole. The nystatin-treated group had poor outcomes in terms of both clinical (52%) and mycologic (6%) responses.

Potential explanations for the differences in efficacy did not appear to include compliance. The oral suspension form of fluconazole may have optimized the total drug exposure to the oral mucosa by both topical and systemic pharmacokinetics [9]. Differences in the antifungal activity of the drugs may also be a factor. Whether other forms of topical nystatin (pastilles and timed-released forms) can perform better remains to be evaluated. With respect to the culture data, fluconazole was shown to be more effective than nystatin in this regimen in eradicating Candida species from the oral pharynx by the end of 2 weeks of therapy. This mycologic cure is temporary but likely explains the longer duration of benefit (i.e., fewer relapses occurred by day 28, 2 weeks after the end of therapy).

On the basis of data from this study and our previous study [8], fluconazole in a tablet or liquid-suspension form and topical clotrimazole troches are clinically equally effective. Therapy with fluconazole suspension may well be targeted for pediatric patients or patients in intensive care units who have nasogastric tubes through which the suspension can be administered.

The choice between the use of fluconazole or clotrimazole troches in the treatment of thrush will depend on factors other than efficacy and should be individualized on the basis of cost, ease of administration, compliance, and clinical resistance. Future studies to further define optimally effective treatments for oral candidiasis, with observations on emergence of resistance, the level of CD4 lymphocyte counts, and cost, seem worthy projects and can clearly influence the choice of drugs for this infection.

Most patients who have oral candidiasis have a clinically minor infection, and the topical agents such as clotrimazole and nystatin are typically used as treatment. This large, prospective comparative study shows a statistically significant clinical difference in outcome, with liquid nystatin clearly inferior to fluconazole oral suspension. The study indicates that when topical agents are used, liquid nystatin in a swish-retain-swallow regimen is not an optimal treatment for oral candidiasis in patients with AIDS.

References