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A comparison of fluconazole oral suspension and amphotericin B oral suspension in older patients with oropharyngeal candidosis

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Abstract

Background: the optimum treatment for oropharyngeal candidosis, particularly in older patients, has not been established. Local treatment with nystatin and amphotericin B can be problematic. The oral suspension formulation of fluconazole may offer a good alternative to these conventional agents.
Objective: to compare the safety and efficacy of fluconazole oral suspension with amphotericin B oral suspension in the treatment of older patients with oropharyngeal candidosis.
Design: randomized open-label study.
Patients: three hundred and five patients, aged 62 or older, with at least one sign or symptom of oropharyngeal candidosis.
Methods: we evaluated patients for the signs and symptoms of candidosis before receiving the study drug and on days 4, 7 and 14. We assessed patients who were cured or improved after 7–14 days of treatment 2 weeks after the end of treatment (follow-up). We obtained specimens from buccal lesions for microscopic examination (baseline only) and culture at baseline and on days 7 and 14. Patients were evaluated for adverse events on days 4, 7 and 14.
Results: one hundred and fifty patients received fluconazole and 155 received amphotericin B. There were no statistically significant differences in clinical or mycological response between fluconazole and amphotericin B at the end of treatment or at follow-up. At the end of treatment, 122 (81%) of 150 fluconazole-treated and 135 (87%) of 155 amphotericin B-treated patients were clinically cured or improved. Mycological cure rates were 35% and 46% for fluconazole and amphotericin B, respectively. The symptoms of burning sensation and buccal pain resolved significantly sooner ($P < 0.05$) in fluconazole-treated patients. The presence of dentures did not affect the response to antifungal therapy. The incidence of adverse events was 46% in the fluconazole group and 50% in the amphotericin B group (not statistically significant).
Conclusion: fluconazole oral suspension is a good therapeutic alternative to amphotericin B oral suspension in the treatment of older patients with oropharyngeal candidosis.

Keywords: *aged, amphotericin B, fluconazole, oral candidosis, suspension*

Introduction

Many factors promote the development of candidosis. Physiological conditions such as pregnancy, infancy and advanced age are risk factors, as are bacterial infections, blood diseases, malignant tumours and treatment with broad-spectrum antimicrobial agents, immunosuppressants and radiation [1–4]. Local conditions such as mucosal irritation by dental prostheses or impaired salivary gland function may also facilitate the development of oropharyngeal candidosis. While oropharyngeal candidosis can affect people of all ages, it is most common at the ends of the age spectrum [1, 4]. In one community hospital, two-thirds of patients with nosocomial candidaemia were over 59, and mortality was higher in older patients [5].

Although oropharyngeal candidosis is generally benign, associated pain and inflammation [4, 6] can

affect quality of life and may even result in reduced food and drug intake. In addition, oropharyngeal candidosis can spread to the oesophagus, which can lead to fungaemia and disseminated candidosis. The optimum treatment for oropharyngeal candidosis, particularly in older patients, has not been established. Treatment with local agents such as nystatin and amphotericin B is effective, but there can be problems with safety, efficacy and compliance [2, 6, 7].

Fluconazole, a triazole antifungal agent active by the oral and intravenous routes, achieves high concentrations in saliva [8–11]. Clinical cure rates of 80–90% have been reported for fluconazole in children with oropharyngeal candidosis [12–16]. A suspension formulation of fluconazole [10, 17–20] allows for more convenient dosing in patients who have difficulty in swallowing tablets or capsules. An additional potential benefit of the suspension formulation in the management of oropharyngeal candidosis is an immediate topical antifungal effect in addition to the sustained systemic effect.

We have compared the safety and efficacy of oral fluconazole suspension with that of oral amphotericin B suspension in the treatment of older patients with oropharyngeal candidosis.

Patients and methods

We conducted this randomized open-label study from May 1996 to February 1998 at 56 investigational sites to compare the efficacy and safety of fluconazole and amphotericin B in older patients with oropharyngeal candidosis. Three hundred and five patients, 62 years of age or older, with at least one sign or symptom of oropharyngeal candidosis, were included. All patients gave written informed consent in accordance with the Declaration of Helsinki (Hong Kong, 1989) before being enrolled in the trial.

Patients already receiving antifungal therapy or who had received antifungal drugs during the 3 days before enrolment were excluded. Patients were also excluded for any of the following reasons: previous participation in this study; participation in another drug study at the time of enrolment or in the month before enrolment; a history of allergy to azole derivatives or agents of the polyene class; treatment with drugs which interact with fluconazole; inability to tolerate oral drug administration; abnormal hepatic function (as determined by a prothrombin time <40% or alanine aminotransferase, aspartate aminotransferase or bilirubin value greater than three times the upper limit of normal); alcohol abuse, drug addiction, psychiatric disorder, inability to co-operate, poor motivation, or any other disorder that would invalidate informed consent. Patients who intended to donate blood within 1 month of the end of the study were also excluded.

At the baseline visit, patients had a physical examination and a medical history was obtained. We graded signs and symptoms of candidosis (burning sensation, buccal pain, dysphagia, erythema or white plaques) according to the following scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe. We graded the severity of oropharyngeal candidosis as follows: 0 = absence of lesions; 1 = the presence of 1 to 4 lesions (mild); 2 = the presence of 5–10 lesions (moderate); and 3 = the presence of lesions over the entire buccal mucosa (severe).

We obtained samples from buccal lesions in all patients and examined them microscopically (potassium hydroxide preparation) to detect yeast and/or hyphae or pseudohyphae. We then inoculated samples on an appropriate solid medium, such as Sabouraud or chloramphenicol agar and sent them to the laboratory for culture at each investigational centre. We obtained blood specimens for determination of prothrombin time and alanine aminotransferase, aspartate aminotransferase, serum bilirubin and serum creatinine concentrations.

We then randomly assigned patients to treatment with either fluconazole (150 patients) or amphotericin B (155 patients) according to a computer-generated randomization schedule.

On study days 4, 7 and 14, we assessed patients for signs and symptoms, adverse events and compliance with the regimen. We obtained blood samples for repeat laboratory testing and swabs or smears of buccal lesions for repeat culture on study days 7 and 14. We evaluated patients who were cured or improved after 7–14 days of study drug treatment about 2 weeks after the end of treatment. At this post-treatment visit, assessments included grading of the signs and symptoms of oropharyngeal candidosis and obtaining swabs or smears of buccal lesions (if still present). We recorded the use of local or systemic antifungal drugs, if any, along with the reason(s) for treatment.

Drug administration

Fluconazole was administered as an oral suspension (10 mg/ml) every 24 h. Patients were instructed to swish 5 ml (50 mg) of fluconazole in the mouth for 1 min then swallow. Any patients who developed renal dysfunction were to have their dosage interval lengthened based on creatinine clearance as follows: 21–40 ml/min, 48 h; 10–20 ml/min, 72 h. Amphotericin B suspension (0.5 g/5 ml) was administered in a dosage of 5 ml (0.5 g) three times daily. Study drug treatment was continued for a minimum of 7 and a maximum of 14 days on the basis of signs and symptoms.

Outcome variables

The primary efficacy measures were clinical and mycological evaluations at the end of treatment (study day 7 or 14).

The investigators categorized the clinical response to treatment as follows: cure (resolution of all signs and symptoms of oropharyngeal candidosis), improvement (reduction in lesions and symptoms but typical oropharyngeal candidal lesions still present) or failure (no change in or progression of the signs and symptoms of oropharyngeal candidosis).

Mycological outcome at the end of treatment was categorized as cure (no lesions or negative culture result for Candida from residual lesions), failure (lesions still present and positive culture result for Candida) or colonization (positive culture result for Candida in the absence of clinical disease).

The secondary efficacy measures included the post-treatment mycological assessment, the frequency of relapse, the frequency of systemic fungal infection and the course of signs/symptoms of oropharyngeal candidosis.

Statistical analysis

We calculated the sample size of this study to be 150 patients per treatment group, or a total of 300 patients. The risk of a type I error was 5% ($\alpha = 0.05$) and the risk of a type II error was 10% ($\beta = 0.10$). We made between-group comparisons using the χ^2 or Fisher's exact test for categorical variables, the Wilcoxon test for ordinal variables and the Student's or Wilcoxon test for quantitative variables depending on distribution. The analysis was performed on data from the intention-to-treat population comprising 150 patients in the fluconazole group and 155 in the amphotericin B group. Statistical significance was declared at the 0.05 level.

Table 1. Demographic and infection characteristics

	Fluconazole ($n = 150$)	Amphotericin B ($n = 155$)
Sex, *n* (%)		
Male	36 (24)	49 (32)
Female	114 (76)	106 (68)
Age, years		
Mean ± SD	84 ± 8	84 ± 8
Range	62–102	62–108
Body mass index, kg/m^2		
Mean ± SD	22.4 ± 4.7	21.7 ± 4.3
Range	12.4–39.0	12.4–30.0
Dentures, *n* (%)	59 (39)	59 (38)
Disease duration, days		
Mean ± SD	6 ± 10	8 ± 17
Sign/symptom score[a] (mean ± SD)		
Burning sensation	1.1 ± 0.9	1.1 ± 0.9
Buccal pain	0.9 ± 0.8	0.9 ± 0.9
Dysphagia	1.0 ± 0.9	0.9 ± 0.9
Erythema	1.9 ± 0.9	1.9 ± 1.0
Plaques	8 ± 1.0	1.6 ± 0.9

SD, standard deviation.
[a]Based on the following grading scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. The range for all signs/symptoms in both treatment groups was 0–3, with no statistically significant difference between the groups (Wilcoxon two-sample test) for any sign/symptom.

Results

The demographic and infection characteristics of the 305 patients enrolled in the study are summarized in Table 1. There were no statistically significant differences between the two treatment groups. The severity of oropharyngeal candidosis among patients in both groups was mild to moderate (mean score 1.6 ± 1.0 for fluconazole and 1.5 ± 0.9 for amphotericin B). Culture results were positive in 129 (87%) of the patients in the fluconazole group and in 133 (86%) of the patients in the amphotericin B group. *Candida albicans* was the most commonly isolated fungal pathogen (Table 2).

The mean duration of treatment was similar for both treatment groups (11.9 ± 3.6 and 11.9 ± 5.6 days for fluconazole and amphotericin B, respectively). Compliance with the treatment regimen was significantly better among fluconazole-treated (95%) than amphotericin B-treated (85%) patients ($P = 0.006$).

Table 2. Candida isolated at baseline from patients with signs/symptoms of oropharyngeal candidosis[a]

	Number of patients (%)	
Pathogen	Fluconazole ($n = 148$)	Amphotericin B ($n = 154$)
C. albicans	98 (76)	111 (83)
C. glabrata	20 (16)	23 (17)
C. tropicalis	10 (8)	7 (5)
C. krusei	5 (4)	5 (4)
C. parapsilosis	3 (2)	2 (2)
C. pseudotropicalis	1 (1)	1 (1)
Candida species	1 (1)	1 (1)
C. guilliermondii	2 (2)	0
C. kefyr	2 (2)	0
C. holmii	1 (1)	0
C. famata	0	1 (1)
C. rugosa	0	1 (1)

[a]Some patients had more than one organism isolated.

Efficacy

Primary measures

Clinical and mycological responses at the end of treatment are summarized in Table 3. There was no statistically significant difference between fluconazole and amphotericin B in terms of either clinical or mycological outcome. Neither was there any difference between the two treatment groups when outcome was analysed according to the most common baseline pathogen, *C. albicans* (Table 3). Other pathogens were too few to analyse formally.

Secondary measures

Two weeks after the end of treatment, 52 fluconazole-treated and 71 amphotericin B-treated patients who were cured or improved at the end of treatment returned for the post-treatment mycological assessment. Of these 123 patients, 25 in the fluconazole group and 43 in the amphotericin B group were not assessed for mycologic response because they no longer had lesions. There was no statistically significant difference between the two treatment groups. Twenty patients in each treatment group had a response of eradication and four patients in each treatment group had colonization. Three fluconazole-treated and four amphotericin B-treated patients experienced recurrence.

The symptoms of burning sensation and buccal pain resolved sooner among fluconazole-treated than amphotericin B-treated patients (Figures 1 and 2). By study day 7, the severity of these symptoms was significantly less ($P = 0.02$; Wilcoxon two-sample test) in the fluconazole than in the amphotericin B treatment group. This difference was not observed on day 14 or the final visit, nor were there any differences between the two treatment groups at any time in dysphagia, erythema or white plaques.

The frequency of relapse of oropharyngeal candidosis was 18% (21 out of 116) in the fluconazole group and 14% (18 out of 128) in the amphotericin B group. This difference was not statistically significant. Twenty-seven of these patients (12 in the fluconazole group and 15 in the amphotericin B group) received antifungal therapy for relapse after the end of study drug treatment.

Response according to risk factors

We analysed clinical and mycological responses at the end of treatment and the mycological response at follow-up according to the risk factors of age, body mass index and denture status. No statistically significant differences were observed between patients who were aged 80 or younger and those aged 85 or older. There also were no significant differences in response to antifungal therapy in patients grouped by body mass index (< 18, 18–22 or >22 kg/m^2).

Of the 176 patients who wore dentures, 151 (86%) were clinically cured or improved at the end of

Table 3. Clinical and mycologic response at the end of treatment: overall and by most common baseline pathogen (*Candida albicans*)

	Number of patients (%)			
	Fluconazole		Amphotericin B	
Response	Overall[a] ($n = 150$)	*C. albicans*[b] ($n = 85$)	Overall[a] ($n = 155$)	*C. albicans*[b] ($n = 99$)
Clinical				
Cure	92 (61)	59 (69)	102 (66)	69 (70)
Improvement	30 (20)	18 (21)	33 (21)	19 (19)
Failure	20 (13)	7 (8)	8 (5)	3 (3)
Not evaluable	8	1	12	8
Mycological				
Cure	52 (35)	35 (45)	71 (46)	45 (45)
Failure	32 (21)	17 (20)	22 (14)	12 (12)
Colonization	46 (31)	28 (33)	41 (26)	32 (32)
Not evaluable	20	2	21	10

[a] $P = 0.13$ (Wilcoxon two-sample test) for overall clinical response; $P = 0.08$ (χ^2) for overall mycologic response.
[b] $P = 0.33$ (Wilcoxon two-sample test) for clinical response by baseline pathogen (*C. albicans*); $P = 0.47$ (χ^2) for mycological response by baseline pathogen (*C. albicans*).

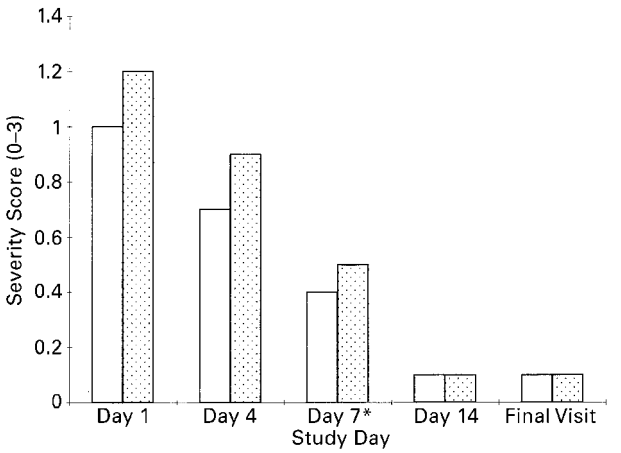

Figure 1. Burning sensation over time during treatment with fluconazole (□) or amphotericin B (▨), graded by the investigator according to the following scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe. Results presented are for patients who had data for all five visits. *$P = 0.02$, fluconazole *versus* amphotericin B (Wilcoxon two-sample test).

treatment compared with 102 (82%) of the 124 who did not wear dentures. Mycological cure rates at the end of treatment were 41% and 40% for patients with and without dentures, respectively. These differences were not statistically significant. Although at the follow-up visit mycological eradication rates were lower (28% and 38% respectively) and colonization

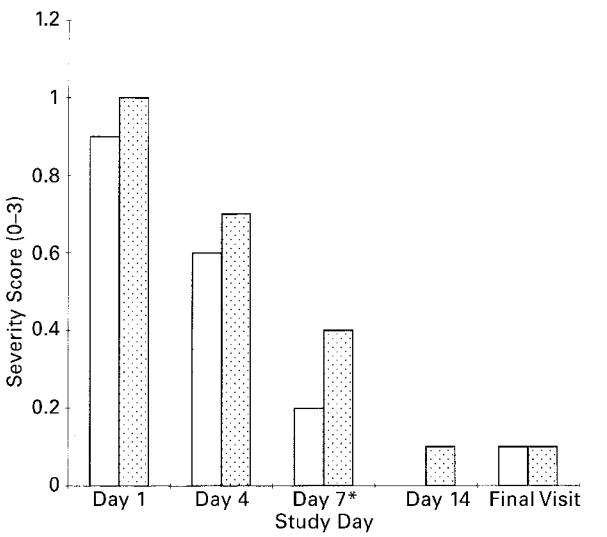

Figure 2. Buccal pain over time during treatment with fluconazole (□) or amphotericin B (▨), graded by the investigator according to the following scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe. Results presented are for patients who had data for all five visits. *$P = 0.01$, fluconazole *versus* amphotericin B (Wilcoxon two-sample test).

Table 4. Adverse events (all causes): reported for 3% of patients

	Number of patients (%)	
	Fluconazole ($n = 150$)	Amphotericin B ($n = 155$)
Urinary tract infection	17 (11)	14 (9)
Death	14 (9)	14 (9)
Diarrhoea	4 (3)	7 (5)
Constipation	2 (1)	7 (5)
Superinfection, bronchial	4 (3)	4 (3)
Dehydration	3 (2)	5 (3)

rates were higher (8% and 4% respectively) in denture wearers compared with subjects who did not wear dentures, these differences were not statistically significant.

Safety

Sixty-nine patients (46%) in the fluconazole group and 77 (50%) in the amphotericin B group experienced at least one adverse event. This difference was not statistically significant. The most frequently reported (3%) adverse events are summarized in Table 4. None of the deaths was attributed to treatment with the study drug; they were related to non-fungal infection, cardiovascular disease, cancer or other chronic diseases. Patients who died during the study were significantly younger (mean age of 80 years) than those who survived (mean age of 85 years; $P = 0.01$).

Six patients had adverse events judged by the investigators to be related to fluconazole, while no adverse events were considered to be related to amphotericin B ($P = 0.01$; Fisher's exact test, two-tail). The six fluconazole-related adverse events included diarrhoea (one patient), nausea and buccal bitterness (one patient), increased liver transaminase concentrations (one patient), aggravation of pre-existing renal dysfunction (one patient) and nausea (two patients). Only the patient with pre-existing renal dysfunction was withdrawn early from the study. No patients were withdrawn because of abnormal laboratory test values.

Discussion

Previous investigators have established the efficacy and safety of fluconazole capsules in the treatment of patients with oropharyngeal candidosis [12–16]. Fluconazole capsules have also been used successfully to treat patients with Candida stomatitis. In a randomized, double-blind, placebo-controlled study [21], fluconazole 50 mg daily for 14 days was significantly ($P < 0.001$) more effective than placebo in reducing inflammation

in patients with Candida-associated denture stomatitis. In addition, clinical response (cure plus improvement) as judged by the investigator was significantly better after treatment with fluconazole than placebo (P = 0.02). This difference was maintained at 2 and 4 weeks after the end of treatment.

The oral suspension formulation of fluconazole provides potential advantages for patients who have difficulty in swallowing tablets or capsules, or for those who have a gastric tube. The bio-equivalence of fluconazole suspension and capsules has been previously demonstrated [10]. The clinical effectiveness of fluconazole suspension has been observed in immunocompromised children [17] and young adults with oropharyngeal candidosis [20]. While a previous study [21] established the effectiveness of fluconazole capsules in patients with Candida-associated denture stomatitis, the present study has demonstrated the effectiveness of fluconazole suspension in older patients with oropharyngeal candidosis. Patients with dentures responded as well as those without dentures.

Amphotericin B suspension is an effective topical agent for patients with oral candidal infections. Poor compliance, however, is common because of the bitter taste and the need for multiple daily dosing [2, 6, 7]. Fluconazole offers the convenience of once-daily dosing, which may explain the better patient compliance observed for fluconazole in this study.

Fluconazole suspension was as effective, both clinically and mycologically, as amphotericin B. The symptoms of burning sensation and buccal pain resolved more quickly during treatment with fluconazole suspension. This rapid resolution of symptoms after therapy with the suspension dosage form is consistent with previous clinical findings.

In an uncontrolled study evaluating the use of fluconazole suspension to treat oesophageal candidosis in patients with AIDS, symptoms resolved in 41% of patients within 1 week and 90% of patients within 2 weeks [18].

Safety data from studies specifically designed to evaluate the use of fluconazole in patients over 65 years of age are scant. In the only study identified from a comprehensive literature search, 50 patients over the age of 65 years with funguria received a 5-day course of oral fluconazole (200 mg initial dose followed by 50 mg per day) [22]. Fluconazole was well tolerated in these older patients, with only three adverse events noted (rash, fatigue and nightmares). Fluconazole also was well tolerated in our large group of older patients who ranged in age from 62 to 102 years. Only one fluconazole-treated patient was withdrawn early from the study due to an adverse event. These safety data combined with the rapid symptomatic response and once-daily dosing indicate that fluconazole suspension is a good therapeutic alternative to amphotericin B in older patients with oropharyngeal candidosis.

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Conflict of interest

E.Y., the lead clinical researcher for this project, works for Pfizer, France. The study was funded by a research grant from Pfizer, France.

Key points

- Fluconazole oral suspension is as effective as amphotericin B oral suspension in the treatment of older patients with oropharyngeal candidosis.
- The clinical symptoms of burning sensation and buccal pain resolved more quickly during treatment with fluconazole oral suspension than with amphotericin B oral suspension.
- Compliance with the treatment regimen was better in patients treated with fluconazole than those treated with amphotericin B.

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Appendix

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