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An open multicentre comparative study of the efficacy, safety and tolerance of fluconazole and itraconazole in the treatment of cancer patients with oropharyngeal candidiasis

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Abstract

Oropharyngeal candidiasis is a frequent infection in cancer patients who receive cytotoxic drugs. In this study, the efficacy, safety and tolerance of fluconazole and itraconazole were compared in non-neutropenic cancer patients with oropharyngeal candidiasis. Of 279 patients who were randomised between the two treatment groups, 252 patients were considered to be eligible (126 in each group). The clinical cure rate was 74% for fluconazole and 62% for itraconazole ($P = 0.04$, 95% Confidence Interval (CI): 0.5–23.3%). The mycological cure rate was 80% for fluconazole and 68% for itraconazole ($P = 0.03$, 95% CI: 1.2–22.6%). The safety and tolerance profile of both drugs were comparable. This study has shown that in patients with cancer and oropharyngeal candidiasis, fluconazole has a significantly better clinical and mycological cure rate compared with itraconazole.

Keywords: Multicentre study; Fluconazole; Itraconazole; Treatment; Cancer patients; Oropharyngeal candidiasis

1. Introduction

Candidiasis is the most common fungal infection in the immunocompromised host, particularly in cancer patients receiving cytotoxic drugs and HIV-patients. Oropharyngeal candidiasis is especially frequent among these patients. This infection is painful, impairs quality of life, and may result in a reduction in food and fluid intake. In addition, extension of oropharyngeal candidiasis to the oesophagus is a common complication, occasionally leading to fungaemia and disseminated candidiasis. The treatment of oropharyngeal candidiasis has been investigated extensively in patients with acquired immunodeficiency syndrome (AIDS) [1–5]. In contrast, in patients with cancer, few studies have addressed the treatment of oropharyngeal candidiasis.

In this study, the efficacy, safety and tolerance of two orally active triazole antifungal agents, fluconazole and itraconazole, were compared. Fluconazole is a triazole, available in oral and parenteral forms, and is effective

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and well tolerated in the treatment of mucosal as well as invasive candidiasis [6–9]. Itraconazole is a broad spectrum triazole, effective against a broad range of fungal pathogens [10,11]. It has been evaluated for the treatment of oropharyngeal candidiasis in doses ranging from 100 to 200 mg/day for 2–4 weeks. In this randomised multicentre study, the efficacy, safety and tolerance of fluconazole (100 mg per day for 10 days) and itraconazole capsules (200 mg per day for 15 days) was compared in patients with non-neutropenic cancer and proven oropharyngeal candidiasis.

2. Patients and methods

Cancer patients aged 16 years or older with signs and symptoms of oropharyngeal candidiasis were randomised after the clinical diagnosis of oropharyngeal candidiasis was confirmed microbiologically. The signs or symptoms included at least one or more of the following: soreness, burning, pain, dysphagia, erythema, or white plaques. A direct microscopic examination taken from an oral swab or scraping was required to show the presence of yeast and/or hyphae or pseudohyphae, and subsequently grow the *Candida* species. Patients with symptoms of oesophagitis could not be entered into the study, unless oesophagoscopy was done and the results for *Candida* were negative. Women of childbearing age must have had a negative blood or urine pregnancy test at baseline. All patients must have given their informed consent.

Exclusion criteria were treatment with any systemic antifungal agent within the previous 7 days, with any topical antifungal agent within the previous 7 days unless there was documented failure with that agent, intolerance or allergy to imidazoles, neutropenia (neutrophil count $\leqslant 500 \times 10^6$ cells/L at entry), inability to take oral medication, HIV infection, malignancy of the head or neck with lesions that might complicate the assessment of response, and moderate or severe liver or renal disease. In addition, patients with oral thrush around a denture, chronic atrophic candidiasis, patients requiring rifampicin therapy, patients with previous entry into the protocol and patients not expected to live 6 weeks were excluded.

After obtaining informed consent, patients were randomised to receive one of two treatments: fluconazole capsules 100 mg per day for 10 days, regardless of meals, or itraconazole capsules 200 mg per day for 15 days, immediately after a meal. During the treatment, clinical and mycological efficacy were evaluated on day 3, 7, 10 and 15. The post-treatment analysis was performed on day 42.

2.1. Evaluation of efficacy

The primary analyses were comparisons of the numbers of patients with clinical cure and with mycological eradication at day 15, time to clinical cure and rate of relapse. Clinical cure was defined as complete resolution of signs and symptoms of oropharyngeal candidiasis, clinical improvement as partial disappearance of baseline signs and symptoms, and clinical failure as no change in or worsening of pre-treatment signs and symptoms. Mycological eradication was defined as eradication of the baseline pathogen based on culture results. Persistence was defined as the persistence of the baseline pathogen on microscopy and/or culture.

Patients in whom clinical cure and microbiological eradication were achieved at the end of treatment were re-evaluated for the efficacy of the treatment strategies on day 42. Cure was defined as complete resolution of signs and symptoms, relapse as typical signs and symptoms of oropharyngeal candidiasis in association with a positive culture for *Candida*.

2.2. Statistical analysis and sample size

For the determination of sample size, based on an estimated clinical efficacy rate for itraconazole of 85%, and an estimated mycological response rate of 65%, 140 evaluable patients per treatment arm were required to detect a difference of 10% for clinical efficacy (95% vs. 85%) and of 15% for mycological efficacy (80% vs. 65%) on fluconazole with a power of at least 0.8, based on a two-tailed test, at a significance level of 0.05.

Efficacy rates and relapse rates were compared using a chi-square test. 95% Confidence Intervals (CI) for the difference between the two treatment groups were calculated based on the normal approximation to the binomial distribution. Duration of survival in the treatment groups was estimated using the Kaplan–Meier product-limit method and compared using the log-rank test. All statistical tests were performed at the 5% significance level and were two-tailed.

3. Results

3.1. Baseline characteristics

From January 1992 to October 1997, 279 patients were randomised to receive either fluconazole or itraconazole. After evaluation, 252 patients were considered to be eligible, 126 in each treatment group (Fig. 1). Twenty-seven patients were not eligible because of absence of *Candida* on direct microscopic examination ($n = 19$), neutropenia at time of randomisation (1), no cancer (1), elevated alkaline phosphatase (1), presence of *Candida* oesophagitis (1), and no clinical reporting form (CRF) submitted (4).

The baseline characteristics and the underlying conditions of the 252 patients are shown in Table 1. The groups were comparable for demographic variables, type of diagnosis and treatment for the underlying disease.

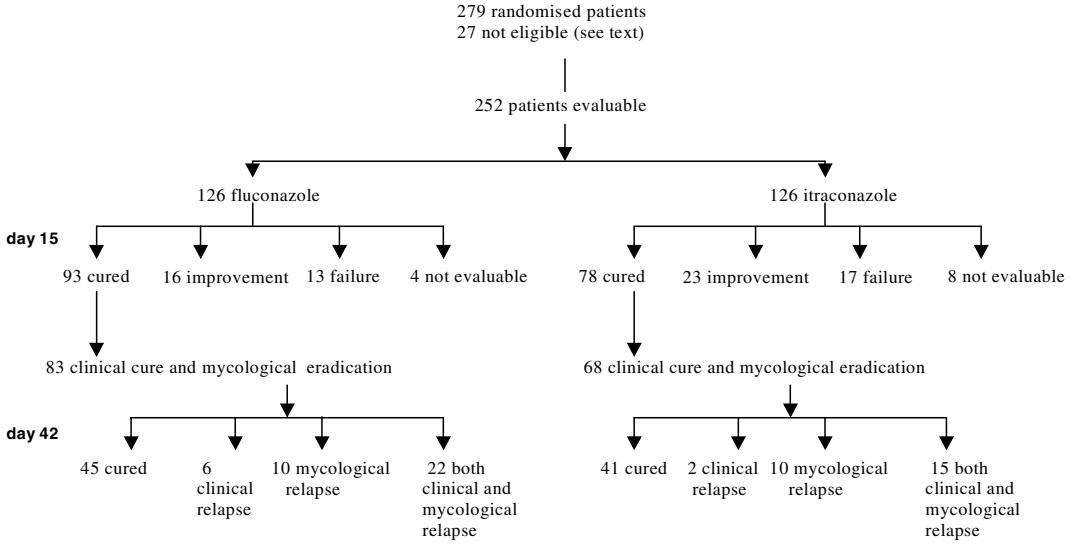

Fig. 1. Trial profile.

Table 1
Baseline characteristics

	Fluconazole ($n = 126$) n (%)	Itraconazole ($n = 126$) n (%)
Age (years), median, range	54 (17–79)	55 (16–89)
Weight (kg) median, range	65 (35–110)	62 (33–97)
Gender: female	67 (53)	55 (44)
Hospitalised	97 (77)	99 (79)
Karnofsky scale, median, range	70 (20–100)	70 (20–100)
Underlying malignant disease/status		
Haematological	9 (7)	9 (7)
Lymphoma	26 (21)	29 (23)
Solid tumour	91 (72)	88 (70)
Bone marrow transplantation		
Allogeneic	2 (2)	1 (1)
Autologous	0 (0)	1 (1)
Cancer treatment		
Cytotoxic therapy	85 (68)	83 (66)
Radiotherapy		
Head and neck	25 (20)	22 (18)
Other site	33 (26)	41 (33)
Corticosteroid use	54 (43)	63 (50)
Antibacterial therapy	46 (37)	46 (37)
Presence of diabetes	15 (12)	14 (11)
PMN within last 14 days		
Falling	15 (12)	11 (9)
Stable	80 (64)	84 (67)
Rising	18 (14)	18 (14)
Unknown	13 (10)	13 (10)
Previous episode of OPC (n)	20	15
Median time interval to current episode (days)	35	33

OPC, oropharyngeal candidiasis; PMN, polymorphonuclear leukocytes.

3.2. Candida infections

The time between onset of signs and symptoms and randomisation for the current episode was 3 days (0–89) for the fluconazole arm and 2 days (0–78) for the itraconazole arm. In 15 patients (12%) in the fluconazole arm, fever (>37.5 °C) was present with a median of 38.3 °C (37.6–39.8 °C). In the itraconazole arm, 18 patients (14%) had fever with a median of 38.1 °C (37.6–39.0 °C).

The most common pathogen isolated was *Candida albicans*, accounting for 97 cases (77%) in the fluconazole arm and 111 cases (88%) in the itraconazole arm ($P = 0.03$, 95%CI, 1.7, 20.5%) (Table 2).

Table 2
Candida species

Candida species	Fluconazole ($n = 126$) (%)	Itraconazole ($n = 126$) (%)
C. albicans	97 (77)	111 (88)
C. tropicalis		1 (1)
C. glabrata	6 (5)	1 (1)
C. krusei	2 (2)	3 (2)
C. parapsilosis	2 (2)	1 (1)
>1 *Candida* species	13 (10)	8 (6)
Other	6 (5)	1 (1)

3.3. Clinical and mycological response

The overall clinical and mycological response to treatment in eligible patients at day 15 is shown in Table 3. In the fluconazole arm, 93 of 126 patients (74%) were clinically cured, compared with 78/126 in the itraconazole arm (62%, $P = 0.04$; 95%CI, 0.5, 23.3%). A favourable response, defined as either clinical cure or clinical improvement, was achieved in 109/126 (87%) patients in the fluconazole arm and in 101/126 (80%) in the itraconazole arm ($P = 0.18$; 95% CI, −2.8, 15.5%).

Mycological eradication in the fluconazole group was achieved in 101/126 patients (80%) compared with 86/126 patients (68%) for itraconazole ($P = 0.03$; 95%CI, 1.2, 22.6%). Clinical cure and mycological eradication was noted in 83 patients in the fluconazole arm (66%) and in 68 patients in the itraconazole arm (54%, $P = 0.054$; 95%CI, −0.1, 23.9%).

Among the patients who had achieved clinical and mycological cure at day 15, a clinical relapse had occurred in 28 out of 83 patients (34%) in the fluconazole group, versus 17 out of 68 patients (25%) in the itraconazole group at day 42 ($P = 0.24$). Mycological relapse occurred in 32 patients (39%) in the fluconazole arm and in 25 patients (37%) in the itraconazole arm ($P = 0.82$), as is shown in Fig. 1. There was no significant difference in the time to relapse between the two treatment arms (data not shown).

3.4. Candida species

The clinical cure rate at day 15 for patients infected with *C. albicans* was 79% in the fluconazole group and 64% in the itraconazole group ($P = 0.014$; 95%CI, 3.4, 27.4%). A clinical favourable response (i.e., complete or partial resolution of signs) was noted in 89 patients (92%) infected with *C. albicans* in the fluconazole arm versus 90 patients (81%) in the itraconazole arm ($P = 0.027$; 95%CI, 1.6, 19.8%). The mycological cure rate for *C. albicans* was 83 out of 97 (86%) in the fluconazole group and 77 out of 111 (69%) in the itraconazole group ($P = 0.006$; 95%CI, 5.1, 27.3%). Of the patients infected with *C. glabrata*, the single patient treated with itraconazole was not evaluable. In the fluconazole group, a clinical favourable outcome was seen in 4 patients (67%) and mycological eradication was seen in 2 cases (33%). Both patients infected with *C. krusei* and treated with fluconazole had a clinical failure, although their cultures became negative. Of three patients with *C. krusei* receiving itraconazole, 2 were clinically and mycologically cured, and one had a failure on treatment. In the subset of patients with multiple *Candida* species, the mycological eradication was similar in both treatment groups (67% for fluconazole vs 63% for itraconazole).

3.5. Mortality

The mortality rate at day 42 was comparable for both groups; 17 patients had died in the fluconazole group (13%) versus 22 in the itraconazole group (17%, log-rank test $P = 0.27$). Thirteen patients (10%) in the fluconazole group died of malignant disease compared with 17 patients (14%) in the itraconazole group. One patient in the fluconazole group and 3 in the itraconazole group died due to non-fungal infectious diseases. In the fluconazole group, three patients died of other reasons including one patient due to bacteraemia and candidaemia, while two patients on itraconazole died

Table 3
Evaluation of treatment efficacy at day 15

	Fluconazole ($n = 126$) (%)	Itraconazole ($n = 126$) (%)	P value
Overall clinical response[a]			
Cure	93 (74)	78 (62)	0.04
Improvement	16 (13)	23 (18)	
Failure	13 (10)	17 (14)	
Not evaluable	4 (3)	8 (6)	
Time to clinical cure (median; min, max)	7 (2–16) days	9 (2–34) days	
Overall mycological response[a]			
Eradication	101 (80)	86 (68)	0.03
Persistence	16 (13)	27 (21)	
Emergence of another species	4 (3)	4 (3)	
Not evaluable	5 (4)	9 (7)	
Time to mycological eradication	4 (3–15) days	4 (1–34) days	

[a] Response rate at Day 15.

due to other reasons. No systemic fungal infections were noted in the itraconazole group.

3.6. Safety and tolerance

Toxicity was reported in 32 patients in the fluconazole arm and in 32 patients in the itraconazole arm. Headache, nausea and vomiting were the most frequent clinical adverse effects. Abnormal liver function tests were noted in 21 patients in the fluconazole group and in 23 patients in the itraconazole group. Of these patients, 12 versus 16 had mild elevation, and 8 versus 7 had moderate elevation of transaminases. One patient treated with fluconazole developed severe liver function test abnormalities, of which the relationship to the antifungal treatment remains unknown. No statistically significant differences were found between the two treatment groups.

4. Discussion

The main conclusion of this study is that fluconazole resulted in a better clinical outcome and mycological eradication compared with itraconazole for the treatment of oropharyngeal candidiasis in non-neutropenic cancer patients.

Several randomised trials have addressed the prevention of candidiasis in neutropenic patients [12,13]. The first trial was a randomised double-blind study which compared fluconazole and itraconazole capsules in preventing fungal infections in neutropenic cancer patients. In that study, no differences were found between itraconazole and fluconazole [12]. The second study compared fluconazole capsules with itraconazole oral solution in neutropenic cancer patients. Both drugs were equally effective in preventing systemic and superficial candidiasis [13].

Treatment modalities of oropharyngeal candidiasis have mainly been studied in AIDS patients. These studies have shown that fluconazole led to a higher cure rate compared with itraconazole capsules after short-term treatment, but both were equally effective in long-term therapeutic efficacy [14]. In a small open-label trial in AIDS patients, a single dose of fluconazole was compared with a 7-day regimen of itraconazole capsules. Fluconazole was significantly more effective than itraconazole at days 8, 15 and 30 [1]. The failures of itraconazole may be explained by drug interactions and the unpredictable absorption of itraconazole capsules [1]. Itraconazole oral solution has been compared with fluconazole tablets in several trials. In two randomised studies among HIV-positive/AIDS patients, itraconazole oral solution and fluconazole tablets were equally effective in treating oropharyngeal candidiasis [4,5]. Likewise, both drugs were effective in HIV-positive patients with oesophageal candidiasis [15]. A favourable clinical efficacy of fluconazole was found in HIV-positive patients with oropharyngeal candidiasis, although long-term suppressive fluconazole therapy may lead to fluconazole-resistant *Candida* strains [16–19]. Likewise, long-term itraconazole prophylaxis may cause *in vitro* resistance against itraconazole [20]. Treatment with either azole may lead to the development of cross-resistance to other azoles [3,20]. In our study, the relapse rate of oropharyngeal candidiasis was quite high, irrespective of the treatment arm. This indicates that in the population of non-neutropenic cancer patients oropharyngeal candidiasis poses a serious clinical problem.

The treatment of oropharyngeal candidiasis in non-neutropenic patients without AIDS has not been previously been investigated in a randomised fashion. The present study suggests that fluconazole capsules are superior to itraconazole capsules in treating non-neutropenic cancer patients with oropharyngeal candidiasis. Although slightly fewer patients had been recruited in this study than planned, the study group was sufficiently large to detect a statistically significant difference between the study arms. In the large subset of patients infected with *C. albicans*, the most common isolate, fluconazole demonstrated a more favourable clinical and mycological outcome than itraconazole. The two patients infected with *C. krusei* and treated with fluconazole had a clinical failure, whereas two of three patients treated with itraconazole were clinically and mycologically cured. These outcomes are in agreement with the notion that *C. krusei* is intrinsically resistant to fluconazole, whereas most isolates are susceptible to itraconazole [21]. Only seven patients in our study were infected by *C. glabrata*. One was randomised to itraconazole and lost to follow-up. Only two of the 6 patients with *C. glabrata* treated with fluconazole were mycologically cured. These results are consistent with variable susceptibility of *C. glabrata* to fluconazole [21]. It has been shown earlier that approximately 40% of the *C. glabrata* isolates resistant to fluconazole are susceptible to itraconazole [21]. Several studies have suggested that itraconazole oral solution is a useful therapy in the treatment of HIV-infected patients with fluconazole-refractory oropharyngeal candidiasis [16,22]. Of note, a greater proportion of patients infected with non-albicans species were randomised to fluconazole. The more favourable efficacy of fluconazole may therefore have been underestimated. In addition, it is unknown whether a higher dose of fluconazole than the 100 mg every day (qd) used in this study may contribute to a better outcome.

This study has two limitations: first the study was not blinded. This could have influenced the reporting of clinical cure rate or adverse effects. The fact that the mycological cure rate of fluconazole was also superior to that of itraconazole (80% versus 68%, $P = 0.03$) suggests that there has been no substantial observer bias. Second,

after this study had been performed, itraconazole has been marketed as an oral hydroxypropyl β-cyclodextrin solution [5,23]. Itraconazole capsules have a variable absorption and should be taken directly after a meal, as their absorption is better at low gastric pH [24,25]. Itraconazole oral solution has been developed to overcome this problem. Although this formulation is now frequently used for treatment of oropharyngeal candidiasis, it has several disadvantages. The taste leads to frequent premature discontinuation, and the soluble form is considered less convenient than capsules in an outpatient situation.

In conclusion, fluconazole showed a favourable clinical efficacy and mycological cure rate for the treatment of oropharyngeal candidiasis in non-neutropenic cancer patients compared with itraconazole. Itraconazole may have an important role in the treatment of oropharyngeal candidiasis caused by fluconazole-resistant *Candida* strains.

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