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Original Paper

A Double-blind Comparison of Fluconazole and Nystatin in the Prevention of Candidiasis in Patients with Leukaemia

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In this multicentre, randomised, double-blind study, the safety and efficacy of oral fluconazole (200 μg/day) and nystatin suspension (6 000 000 IU/day) for the prevention of fungal infections were compared in patients with leukaemia undergoing remission induction chemotherapy. Antifungal prophylaxis was initiated at the time chemotherapy was started and continued throughout the hospital stay or the period of neutropenia to a maximum of 42 days. Prophylaxis was successful (no evidence of fungal infection or fever of unknown origin unresponsive to antibiotics) in 38 of 56 (68%) fluconazole-treated and 25 of 53 (47%) nystatin-treated patients ($P = 0.03$). 2 patients (4%) in the fluconazole group and 6 (11%) patients in the nystatin group developed systemic fungal infections ($P = 0.15$). The overall frequency of adverse events was similar among fluconazole-treated (29%) and nystatin-treated (32%); most events in both treatment groups involved the gastrointestinal tract. These results indicated fluconazole was more effective than nystatin in preventing *Candida* infections in patients with leukaemia; fluconazole was well tolerated. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: fluconazole, nystatin, leukaemia, fungal infections, prophylaxis
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INTRODUCTION

SUPERFICIAL AND systemic fungal infections have become a significant cause of morbidity and mortality in neutropenic patients with acute leukaemia [1–3]. Because colonisation of the alimentary tract is assumed to precede systemic fungal infections [4], a reasonable approach to reducing infection would be eradication of this reservoir for infection. Amphotericin B, the so-called gold standard of antifungal therapy, has been generally successful as empiric or prophylactic therapy [4, 5]. This drug, however, is poorly tolerated when administered orally or intravenously due to its bitter taste and systemic toxicity, respectively. In addition, breakthrough infections have been reported [2, 4, 6]. Another nonabsorbable antifungal agent, nystatin, often is administered orally for the prevention of candidiasis in immunocompromised patients [7]. Similar to oral amphotericin B, nystatin is poorly tolerated and its effectiveness in preventing systemic infection is dubious [8].

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Owing to its favourable pharmacological pharmacokinetic characteristics as well as its good safety profile, fluconazole holds promise in prophylactic antifungal therapy. Fluconazole demonstrates *in vitro* activity against many common fungal pathogens associated with invasive infections in cancer patients [9]. Its pharmacokinetic profile is characterised by consistent absorption, even in patients with compromised gastrointestinal function, extensive distribution throughout the body, and an extended plasma elimination half-life that allows once-daily administration [9, 10]. In preclinical studies, fluconazole was effective in preventing disseminated candidiasis in persistently granulocytopenic rabbits [11]. Fluconazole is generally well tolerated [9].

In clinical trials involving neutropenic patients with cancer, fluconazole was shown to be as effective as intravenous or oral amphotericin B in decreasing the incidence of fungal infection [12, 13] and more effective in this regard than oral polyenes [14], oral imidazoles [15], or placebo [16–18]. Fluconazole also was better tolerated than amphotericin B [12, 13]. Several of these studies [12,16–18] evaluated daily fluconazole doses of 400 mg administered orally or intravenously, while others investigated doses of 50 to 200 mg [13–

15]. Despite the success observed with fluconazole, there is still some concern regarding the emergence or development of resistant strains during the prophylactic use of antifungal agents [1, 16, 19–21].

The purpose of the present study was to compare the safety and efficacy of oral fluconazole (200 mg/day) with that of nystatin suspension (6 000 000 IU/day) for the prevention of fungal infection in patients with leukaemia receiving remission-induction chemotherapy. Results of a previous study [15] showed 200 mg/day to be an effective prophylactic dosage of fluconazole that did not result in the emergence of non-*albicans* species of *Candida*. Fluconazole has been compared with oral amphotericin B in a separate study (not yet analysed).

PATIENTS AND METHODS

Study design and drug administration

This was a multicentre, randomised, double-blind, parallel-group, comparative study conducted in Australia, Belgium, Canada, Germany, Korea, and Spain. Fluconazole was provided as a 100 mg capsule; a matching placebo capsule was identical in appearance to the fluconazole capsule. Nystatin was provided as a suspension (100 000 IU/ml) in 60 ml bottles; placebo suspension, identical in appearance to nystatin suspension, also was provided in 60 ml bottles. Prophylactic treatment with study drug began at the start of chemotherapy and was continued throughout the hospital stay or the period of neutropenia (defined as 1000 neutrophils/mm^3 or less) to a maximum of 42 days. Patients randomly assigned to treatment with fluconazole received two fluconazole capsules at the same time each day and a 10 ml dose of placebo suspension six times daily. Those randomly assigned to prophylaxis with nystatin received two placebo capsules and nystatin suspension at the same dosing intervals described for fluconazole-treated patients. If a patient developed renal insufficiency, the dosing interval for the capsule (fluconazole or placebo) was extended to 48 h (creatinine clearance of 21–40 ml/min) or 72 h (creatinine clearance of 10–20 ml/min). Patients did not receive concomitant treatment with growth factors since such therapy was not yet widely available at the time the study was conducted (January 1991–November 1992).

Patients

Adult male and female patients with leukaemia, 16–80 years of age, who were scheduled to undergo either initial or repeat remission induction chemotherapy were eligible for enrolment in this trial. Patients who were previously enrolled in this study were allowed to enrol again provided that, at the time of second enrolment, a minimum of 2 months had passed since the previous course of chemotherapy. Patients who had positive oropharyngeal cultures were eligible to participate unless thrush was documented by pseudohyphae on microscopy and oropharyngeal lesions deemed to be characteristic of thrush. Pregnant or lactating women, patients with a documented fungal infection requiring antifungal therapy, those with AIDS or AIDS related complex (ARC) or known to be HIV-positive, and those with a history of allergy to azole compounds or nystatin were excluded from enrolment in the study. Also excluded were patients taking other investigational drugs except those used in cancer chemotherapy for which the safety profile had been well established, patients who had received any antifungal drug (except topical agents for dermatological or vaginal infections) within 1 week before enrolment in this study, and patients with renal or hepatic disease before receiving study drug therapy as determined by serum creatinine above 3 mg/dl, or an elevated liver function test (alanine aminotransferase, ALT; aspartate aminotransferase, AST; lactate dehydrogenase, LDH; or alkaline phosphatase) value greater than three times the upper limit of normal, or serum bilirubin greater than 3 mg/dl. Patients enrolled in the study must have been able to swallow a capsule and a suspension. Patients or their legal guardians gave informed consent in accordance with the Declaration of Helsinki, 1983.

Efficacy assessments

Prophylaxis with study drug was considered successful if none of the following occurred: (1) documented systemic fungal infection proven by biopsy or culture, or in the case of death, documentation at autopsy, if performed; (2) documented *Candida* oesophagitis proven by culture and barium swallow or oesophagoscopy; (3) documented oropharyngeal candidiasis proven by culture and microscopy in the presence of symptoms not attributed to other pathology; and (4) development of fever of unknown origin (FUO) with body temperatures of 38°C or higher that failed to respond to antimicrobial therapy after a minimum of 48 h (or which initially responded, but a new fever with an oral temperature spike of 38°C or higher developed, lasting for 2 days) and required initiation of empiric systemic antifungal therapy for suspected fungal infection. This study was designed to compare preventive rather than therapeutic outcome, and therefore therapeutic efficacy was not assessed. Colonisation was assessed by comparing baseline and end of therapy cultures.

Statistical methods

Baseline characteristics were compared between treatment groups using Fisher's exact test for multi-way tables for race and sex and two-sample *t*-test for age and weight. The distribution of clinical efficacy (response to prophylaxis) at the end of therapy, the proportion of patients who experienced study drug-related or possibly study drug-related adverse events, and the proportion of patients with clinically significant treatment-related laboratory abnormalities were compared between treatment groups using Fisher's exact test. Changes in neutrophil count from baseline to end of therapy were compared between treatment groups using the *t*-test. All statistical tests were two-tailed and performed at the 5% significance level.

RESULTS

A total of 164 patients were enrolled in the study and randomly assigned to treatment with either fluconazole (86 patients) or nystatin (78 patients). The demographic characteristics of these patients are summarised in Table 1. There were no statistically significant differences between the two treatment groups in any of the demographic parameters. 21 (24%) patients in the fluconazole treatment group and 22 (28%) in the nystatin treatment group discontinued therapy early for various reasons (Table 2). The most common reason for premature discontinuation of study drug therapy was adverse events. Data for 30 fluconazole-treated and 25 nystatin-treated patients were excluded from the efficacy analysis (Table 3). Therefore, 56 patients in the fluconazole group and 53 in the nystatin group were evaluable for the efficacy

Table 1. *Demographic characteristics*

	Fluconazole ($n=86$)	Nystatin ($n=78$)
Age		
Mean (S.D.)	4.28 (17.1) years	43.7 (16.8) years
Range	17–79.8	17–80.0
Sex		
Male	41 (48%)	42 (54%)
Female	45 (52%)	36 (46%)
Race		
White	49 (57%)	47 (60%)
Asian	35 (41%)	29 (37%)
Other	2 (2%)	2 (3%)
Height		
Mean (S.D.)	165.9 (8.5) cm	166.6 (9.8 cm)
Weight		
Mean (S.D.)	65.3 (12.7) kg	67.5 (13.6) kg
Diagnosis		
Acute myeloid leukaemia	61 (71%)	51 (65%)
Acute lymphoid leukaemia	20 (23%)	21 (27%)
Chronic myeloid leukaemia	1 (1%)	1 (1%)
Other*	4 (5%)	5 (6%)

*Other includes leukaemia unspecified cell not otherwise specified (1, nystatin); acute leukaemia not otherwise specified (2, fluconazole); lymphomas not elsewhere classified (1, fluconazole; 2, nystatin); multiple myeloma (1, nystatin); carcinoma *in situ* bronchus/lung (1, nystatin); malignant neoplasm thymus (1, fluconazole). S.D., standard deviation.

analysis. One patient in the fluconazole group was lost to follow-up after the baseline visit; therefore, 85 fluconazole-treated and 78 nystatin-treated patients were included in the analysis of adverse events. The mean duration of therapy for evaluable patients who received fluconazole or nystatin was 28.7 (standard deviation (S.D.) 10.4) days and 25.3 (S.D. 10.6) days, respectively. The mean daily dose was 197 (S.D. 13.7) mg for fluconazole and 57.7 (S.D. 5.5) ml for nystatin.

Efficacy

Clinical outcome at the end of prophylaxis is presented in Table 4. Fluconazole was significantly more effective ($P=0.03$) than nystatin in preventing candidiasis. Most patients who failed prophylaxis in both treatment groups developed fever on unknown origin (FUO) and required empiric systemic antifungal therapy. No differences were noted between fluconazole-treated and nystatin-treated patients in terms of the frequency or pattern of colonisation with *C. albicans* and non-*albicans* species (data not shown). Results of analysis of data for an intent-to-treat population, including all patients who received at least one dose of study medication and had an end-of-prophylaxis assessment, were consistent with those of the evaluable population although the difference was not significant ($P=0.1$). In the intent-to-treat population, prophylaxis was successful in 56 of 82 (68%) fluconazole-treated and 42 of 76 (55%) nystatin-treated patients.

The neutrophil count for evaluable patients in both treatment groups was compared at baseline and at the end of prophylaxis (data not shown). There were no statistically significant differences between the two treatment groups with respect to the mean neutrophil count at baseline or the mean decrease in neutrophil count from baseline to the end of therapy.

Adverse events

25 of 85 (29%) patients in the fluconazole group and 25 of 78 (32%) patients in the nystatin group experienced at least one adverse event rated by the investigators as related or possibly related to study drug therapy, a difference that was

Table 2. *Summary of patients who discontinued study drug therapy prematurely*

Reason	Fluconazole	Nystatin
Intercurrent illness	2	4
Poor compliance	5	1
Adverse event(s)*	9	13
Other		
Insufficient treatment/failure	2	0
Oropharyngeal candidiasis at time of enrolment	1	0
Death due to sepsis	1	0
Patient requested discharge against medical advice	0	2
Refractory neutropenia	0	1
Not specified	1	1

*All causalities. For related or possibly related adverse events, 6 patients in the fluconazole group and 11 in the nystatin group discontinued study drug therapy early. See text for details.

Table 3. *Summary of reasons for exclusion from efficacy analysis*

	Number of patients	
Reason	Fluconazole	Nystatin
Did not meet entry criteria	6	6
Incorrect dosing	12	0
Withdrawn due to patient request	0	1
Poor compliance	3	1
Early withdrawal—adverse event	6	10
Early withdrawal—intercurrent illness	2	2
Insufficient treatment period	0	1
Took prohibited concomitant medication	1	3
Lost to follow-up	0	1
Total number of patients	30	25

Table 4. *Clinical outcome at the end of prophylaxis (evaluable patients)*

	Fluconazole (n=56) n (%)	Nystatin (n=53) n (%)
Successful prophylaxis	38 (68)*	25 (47)
Unsuccessful prophylaxis	18 (32)	28 (53)
Oropharyngeal candidiasis	3 (5)	3 (6)
Oesophageal candidiasis	0	0
Systemic candidiasis†	2 (4)	6 (11)
FUO and empiric systemic antifungal therapy	14 (25)	19 (36)

*P=0.03 for fluconazole versus nystatin; Fisher's exact test (two-tail).
†Includes 1 nystatin-treated patient who had undocumented *Candida* oesophagitis and was considered by the investigator to be a prophylactic failure. Also includes 1 fluconazole-treated patient who had a skin lesion that was culture-positive for *Aspergillus*. FUO, fever of unknown origin. One fluconazole-treated patient who had both documented systemic and oropharyngeal candidiasis is counted in each category.

not statistically significant (Table 5). The most common adverse events in both treatment groups were associated with the gastrointestinal tract, and a total of 15 patients (6 in the fluconazole group and 9 in the nystatin group) discontinued study drug treatment due to such events. Reasons for discontinuation of fluconazole included severe abdominal pain, moderate or severe nausea, severe vomiting, hepatic function abnormality, and increases in AST and ALT values (refer to discussion on laboratory abnormalities below). Nystatin was discontinued due to moderate or severe vomiting, severe nausea, hepatic function abnormality, and increases in AST and alkaline phosphatase levels. Severe rash was a reason for discontinuation of nystatin in 2 patients, 1 of whom also was discontinued for gastrointestinal problems.

Serious adverse events were reported for 42 patients in this study. Among these serious adverse events, there were 6 patient deaths in the fluconazole group and 11 patient deaths in the nystatin group. In most cases, death was attributed to the underlying leukaemia or to concurrent/intercurrent non-fungal illness. 2 fluconazole-treated and 3 nystatin-treated patients had fungal infections when death occurred. The 2 patients in the fluconazole group developed *Aspergillus* pneumonia (1 after 29 days and 1 after 18 days of study prophylaxis). Both patients died despite initiation of treatment with amphotericin B. One patient in the nystatin group, who developed *C. tropicalis* septicaemia after 4 days of study prophylaxis, died approximately 2 weeks later, 5 days after treatment with amphotericin B was initiated. The 2 other patients in the nystatin group died after discharge from the study (1 after 5 weeks and 1 after 10 days); deaths were attributed to fungal infection and fungal pneumonia. Other serious adverse events not resulting in death (reported for 15 fluconazole-treated and 10 nystatin-treated patients), included septicaemia, septic shock, complications associated with various concurrent/intercurrent diseases, and adverse events attributed to concomitant medications. One of these nystatin-treated subjects developed oesophageal candidiasis after 11 days of study prophylaxis. Serious adverse events (bacterial septicaemia and respiratory distress syndrome) were reported after discharge from the study.

Table 5. *Related or possibly related adverse events*

Body system preferred term	Fluconazole (n=85) n (%)	Nystatin (n=78) n (%)
Gastrointestinal*	16 (19)	17 (22)
Abdominal pain	4 (5)	1 (1)
Alkaline phosphatase increased	0	1 (1)
ALT increased	1 (1)	2 (3)
AST increased	1 (1)	1 (1)
Constipation	1 (1)	0
Diarrhoea	1 (1)	0
Hepatic function abnormal	1 (1)	1 (1)
Hepatitis	1 (1)	1 (1)
Hepatocellular damage	1 (1)	0
Nausea	5 (6)	6 (8)
Vomiting	4 (5)	9 (12)
CNS	1 (1)	4 (5)
Dizziness	0	3 (4)
Hypoesthesia	0	1 (1)
Insomnia	1 (1)	0
Dermatological	4 (5)	5 (6)
Rash	2 (2)	5 (6)
Rash, erythematous	1 (1)	0
Rash, maculopapular	1 (1)	0
Eye, ear, nose, throat	1 (1)	0
Taste perversion	1 (1)	0
Metabolic and nutritional system	2 (2)	1 (1)
Enzyme abnormality	2 (2)	1 (1)
Miscellaneous	2 (2)	4 (5)
Asthenia	1 (1)	1 (1)
Chest pain	1 (1)	0
Fever	0	2 (3)
Pain	0	1 (1)
Patients with at least one adverse event	25 (29)	25 (32)
Number of adverse events	30	36

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system *Some patients had more than 1 gastrointestinal adverse effect

A number of clinically significant laboratory test abnormalities were reported during this study; however, most were attributed to concomitant medications or the underlying leukaemia. Laboratory test abnormalities considered by the investigators to be possibly related to study drug therapy were reported for 24 patients in the fluconazole group and 39 in the nystatin group. The most common abnormalities were elevations in AST (2 fluconazole; 6 nystatin), ALT (7 fluconazole; 19 nystatin), and alkaline phosphatase (6 fluconazole; 4 nystatin) values. In the fluconazole group, the most abnormal ALT value was 10 times the upper limit of the normal range, whereas in the nystatin group the most abnormal value was 23 times the upper limit of normal. Values for AST were 3–4 times and 2–11 times the upper limit of normal for fluconazole and nystatin, respectively. One patient in each treatment group was withdrawn from the study due to an elevated liver enzyme (fluconazole: increased AST and ALT; nystatin: increased alkaline phosphatase and AST). Other less frequently reported possibly study drug-related laboratory test abnormalities in both treatment groups included abnormal haematocrit, platelet count, lymphocyte count, LDH, blood urea nitrogen, serum creatinine, total protein, and serum albumin. In addition, abnormalities in sodium, potassium, haemoglobin, red blood cell count, white blood cell count, neutrophil count, monocyte count and gamma-glutamyl transpeptidase were reported for nystatin-treated patients.

DISCUSSION

A key objective in the management of patients with leukaemia continues to be reduction of the morbidity and mortality associated with infectious complications, including invasive fungal infections. Fungal infection has emerged as a menacing challenge in the management of neutropenic patients with leukaemia [1, 3, 19] presumably due to such contributing factors as intensive chemotherapy regimens, widespread use of central venous catheters, and the success of empiric antibiotic therapy. Once established, disseminated fungal infections in neutropenic patients seldom respond to systemic antifungal therapy. In addition, early diagnosis of invasive fungal infection in neutropenic patients is often difficult and unreliable [1, 22] with discovery only at autopsy in many cases [3, 23].

Because diagnosis is unreliable and mortality is high in patients with prolonged neutropenia who develop deep fungal infection, initiation of empirical antifungal therapy has

become a standard procedure in patients whose fever persists despite empirical antibiotic therapy [5, 24]. High mortality rates have been reported among immunocompromised patients with fungaemia who received amphotericin B therapy [25]. In a series of 410 patients with haematological malignancies [3] more than half the patients who died due to documented systemic fungal infection had received empirical therapy with amphotericin B. The limited success observed with empirical antifungal therapy suggests that alternative measures are needed.

Based on the considerations outlined above, antifungal chemoprophylaxis, which would preclude the need for empirical antifungal therapy, appears to be a reasonable approach for patients with acute leukaemia undergoing induction therapy [26]. By reducing the burden of *Candida* in the alimentary tract, the predicted outcome of antifungal prophylaxis would be a lower incidence of candidaemia and disseminated candidiasis [4]. While amphotericin B is the accepted standard of treatment for most types of systemic fungal infections in patients with leukaemia, its use is limited by potentially serious adverse effects. Lipid formulations of amphotericin B appear to reduce some of these adverse effects, including nephrotoxicity. It remains to be proven, however, whether these lipid formulations offer any benefit over conventional amphotericin B in terms of outcome. The triazole antifungal agents have been associated with less toxicity, and agents such as fluconazole and itraconazole have become accepted therapy for patients with selected mycoses [27].

In the present study, prophylaxis with fluconazole (200 mg/day) was more effective than oral nystatin (6 000 000 IU/day) in reducing the overall incidence of fungal infections in patients with leukaemia undergoing induction chemotherapy. The success rate for fluconazole observed in this study (68%) is consistent with, albeit somewhat lower than, results (80–97%) reported in other studies evaluating fluconazole prophylaxis in immunocompromised patients [12–18]. The fluconazole dosage used in four of these seven studies was 400 mg/day, administered orally or intravenously [12, 16–18]; the other studies used various lower dosages. Differences in dosage and/or study methodology may explain the differences in success rates.

Reasons for the persistence of *Candida* despite the use of fluconazole have not been completely elucidated. One possibility is the development or emergence of fluconazole-resistant organisms, such as *C. krusei* or *C. glabrata*, during chemoprophylaxis in immunocompromised patients [1, 21, 28]. This interpretation may be limited, however, because *in vitro* susceptibility test results may not always correlate with clinical success [28]. Furthermore, invasive infection due to *C. krusei* has been reported in immunocompromised patients not treated with fluconazole [29] as well as in those treated with amphotericin B [6, 13]. In the present study, the patterns of colonisation at the end of treatment were similar in both treatment groups. These findings are in agreement with those of other studies in which there was no increased incidence of colonisation or infection by either *C. krusei* or *C. glabrata* in patients with leukaemia who received fluconazole prophylaxis [13, 15, 17].

An additional concern raised by some investigators [30] is whether azole antifungal prophylaxis can prolong the duration of severe neutropenia in immunocompromised patients. The mean number of days during which the neutrophil count was less than 0.1×10^9/l was somewhat longer among patients who received ketoconazole (11.3 days) compared with those who received oral amphotericin B plus nystatin (8.6 days) [31]. In a placebo-controlled study [32], the duration of severe neutropenia ($<0.1\times10^9$/l) was significantly ($P=0.04$) longer in the ketoconazole group (36% of treatment time) than in the placebo group (26% of treatment time). In contrast, no differences in the pattern of the decline or recovery of the neutrophil count were observed between patients with leukaemia who received fluconazole and those who received placebo in two large-scale multicentre studies [16, 17]. Based on the findings in these studies [16, 17] as well as our own results, it appears unlikely that fluconazole has any adverse effect on the recovery from immunosuppression.

Both fluconazole and nystatin were well tolerated in this high-risk group of patients with leukaemia. The adverse events reported in both treatment groups were primarily gastrointestinal in nature. More nystatin-treated patients than fluconazole-treated patients discontinued study drug therapy early due to a drug-related or possibly drug-related adverse event.

In summary, oral fluconazole administered in a dosage of 200 mg/day was more effective than nystatin (6 000 000 IU/day) in preventing documented and presumed *Candida* infections in patients undergoing remission induction chemotherapy for acute leukaemia. Fluconazole was well tolerated.

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APPENDIX: THE ANTIFUNGAL PROPHYLAXIS STUDY GROUP

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