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Fluconazole versus itraconazole for the prevention of fungal infections in haemato-oncology

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Abstract

***Aims*—To compare the efficacy of and tolerance to oral fluconazole and intraconazole in preventing fungal infection in neutropenic patients with haematological malignancies.**

***Patients*—213 consecutive, afebrile adult patients treated with or without autologous stem cell transplantation for haematological malignancies.**

***Methods*—A randomised, double blind, single centre study. Patients were randomly assigned to receive fluconazole 50 mg or itraconazole 100 mg, both twice daily in identical capsules. An intention to treat analysis was performed on 202 patients, 101 in each group.**

***Results*—Microbiologically documented systemic fungal infections occurred in four patients in each group. Clinical fungal infection was thought to be present in seven recipients of fluconazole and four of itraconazole. In all 202 patients, 29 proceeded to intravenous amphotericin (amphotericin B), 16 in the fluconazole group and 13 in the itraconazole group. Superficial fungal infection was seen only in three non-compliant patients in the fluconazole group. All these infections were oral. No major differences were noted in the isolates of fungi in mouth washes and fecal samples. Overall mortality was 8.9% (18 deaths; seven in the fluconazole group, 11 in the itraconazole group). Mortality from microbiologically and clinically documented fungal infection was 4.5% (nine deaths; three in the fluconazole group, six in the itraconazole group). Median time to suspected or proven fungal infection was 16 days in both groups. None of these comparisons reached statistical significance ($p < 0.05$). No major clinical toxicity was noted and compliance was excellent.**

***Conclusions*—In neutropenic patients treated for haematological malignancies with or without autologous stem cell transplantation, fluconazole and itraconazole in low doses result in a similar low frequency of fungal disease. Fluconazole may be the preferable drug because of the smaller number of capsules and lack of need for timing relative to meals.**

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Superficial and disseminated fungal disease remains a challenging problem for clinicians caring for neutropenic patients with haematological malignancies.[1–4] It is the most important cause of morbidity and mortality, and because it is difficult to detect, most centres give intravenous antifungal agents to febrile patients who do not readily respond to antibacterial treatment.[5–7]

Antifungal prophylaxis is widely used. Oral amphotericin has been used in doses of around 1 to 3 g daily. Its acceptability to patients is poor. In randomised trials, oral polyenes did not prevent haematogenous candidiasis.[8–11] Fluconazole has emerged as the most widely used prophylactic agent in neutropenic patients. The drug effectively prevents oropharyngeal candidiasis. In doses of 400 mg daily, it was shown to reduce fungal colonisation, candidiasis, and mortality in two randomised trials.[12 13] The optimal dose remains to be determined. In both single arm and randomised trials, doses as low as 50, 100, and 200 mg daily were associated with a very low incidence of superficial and systemic candidiasis.[14–17] A drawback of fluconazole prophylaxis is its lack of activity against *Aspergillus* spp.

Itraconazole, another imidazole, has in vitro and in vivo activity against *Aspergillus* spp.

An important limitation is its erratic bioavailability in certain settings.[18 19] Rather limited data are available regarding its efficacy in prevention of fungal disease in neutropenic patients. In a small double blind trial, 200 mg of itraconazole twice daily had no additional benefit over oral amphotericin with respect to preventing aspergillosis.[20]

We decided to compare fluconazole 100 mg daily with itraconazole 200 mg daily in a double blind, randomised trial in patients with haematological malignancies.

Methods

Eligible patients included consecutive adults who had a haematological malignancy and were to receive cytotoxic treatment likely to induce neutropenia (neutrophil count $< 0.5 \times 10^9$/l) with a duration of at least 10 days. All patients were treated according to protocols of the Dutch Cooperative Haematooncological Study Group (HOVON) or received high dose chemotherapy with autologous stem cell rescue, or both.

Patients were excluded if they were younger than 18 years, if they were known to have hypersensitivity to triazoles, if they were treated with antifungal agents in the previous 14 days, or if there was overt infection.

STUDY PROTOCOL

After informed consent was obtained according to the protocol of the ethics committee of our institution, patients were randomised to receive 50 mg of fluconazole or 100 mg of itraconazole twice daily. Study drugs were given in identical capsules, in a double blind fashion, directly after a meal. All patients received ciprofloxacin 500 mg twice daily and roxitromycine 150 mg twice daily, both orally. Nasal amphotericin was also given, 2 mg three times daily into both nostrils. All these four prophylactic drugs were given from the day of start of chemotherapy until the neutrophil count was above 0.5×10^9/l. A single lumen subclavian intravenous catheter was inserted, and the dressing was renewed daily. Antiviral treatment with acyclovir, leucocyte-poor erythrocyte concentrates, and platelets was given as clinically indicated.

Granulocyte transfusions were not used. Granulocyte colony stimulating factor (G-CSF) was given according to protocols. Patients were nursed in conventional single or double rooms, and patients receiving autologous stem cell transplantation after busulphan-cyclophosphamide conditioning (for acute leukaemia and multiple myeloma) were treated in down flow isolation rooms.

All patients were examined daily for clinical signs of infection. When the axillary temperature increased to more than 38.5°C or other signs of infection appeared, samples for microbiological cultures, including at least two separate blood specimens, were obtained, one of which was withdrawn through the intravenous catheter. Treatment with imipenem-cilastatin 500 mg four times daily intravenously was started. If fever persisted, vancomycin 1 g twice daily intravenously was added after 72 hours. Empirical treatment with amphotericin, 0.7 mg/kg, was added to the imipenem-cilastatin plus vancomycin combination if fever persisted for another 72 hours. Vancomycin with or without amphotericin was given earlier if cultures so dictated.

At the beginning of intravenous antibiotic treatment, and thereafter every three days, chest and sinus *x* rays were obtained and other relevant investigations performed for the duration of the febrile period. Blood cultures were drawn every third day and whenever axillary temperature rose above 38.5°C.

To compare the efficacy of and tolerance to fluconazole and intraconazole, the following variables were measured: microbiologically documented bacterial or fungal infection, clinically documented infection, superficial clinically overt and culture documented fungal infection, fever of undetermined origin (FUO), time to empirical antifungal treatment with amphotericin, compliance, treatment interruption caused by side effects, mortality, and plasma concentrations of fluconazole, itraconazole, and hydroxyitraconazole. The latter were determined once weekly, 10 hours after administration of the study drug.

DEFINITION OF INFECTION

Microbiologically documented infection was defined as infection established by one positive culture of sputum, bronchiolar alveolar lavage, tissue biopsy, or blood. For coagulase negative staphylococci or candida septicaemia to be diagnosed, two separate positive blood cultures were required.

Clinically documented infection was defined whenever typical signs of infection were found on physical examination, *x* rays, or other imaging tests without positive cultures. Those were judged to be bacterial when they responded to intravenous antibiotic treatment and to be fungal when they persisted during antibiotic treatment and required empirical amphotericin treatment. FUO was defined as every febrile episode without microbiologically or clinically documented infection, whether the episode led to amphotericin treatment or not.

COMPLIANCE

Compliance was monitored by the attending nurses. It was deemed good if a patient missed fewer than 20% of the total number of doses and poor if the patient missed more.

SIDE EFFECTS

Side effects were monitored clinically on the daily rounds by asking about nausea and vomiting related to the administration of the study drug, and by looking for rashes. Serum electrolyte analyses and tests for liver and renal function were done three times weekly.

Oral mouth washes were cultured twice weekly for bacterial and fungal species. Faecal samples were cultured once weekly.

STATISTICAL ANALYSIS

Results in all patients were analysed according to the intention to treat principle. Categorical data were analysed by Fisher's exact test, and the Wilcoxon rank sum test was used for continuous data. The difference between the two groups for the time to suspected fungal infection—defined as the time between starting the study drug and the development of fever requiring amphotericin treatment—was analysed using the log rank test. All analyses were performed using SAS software (SAS Institute, Cary, North Carolina, USA).

Results

In all, we studied 213 patients with haemato-oncological diseases, 107 initially randomly assigned to fluconazole and 106 to itraconazole. Of these, 11 were excluded from analysis. Reasons for exclusion were: chemotherapy not started (1); infection at entry requiring treatment (3); and removal from the protocol because of leakage of sewage pipes in bedroom (7). Thus 101 patients remained in the fluconazole group and 101 in the itraconazole group. The characteristics of the patients are given in table 1. The two groups were comparable for sex, age, type of diagnosis, and number of autotransplants. Duration of neutropenia ($< 0.1 \times 10^9$/l) was slightly longer in the fluconazole group, at 11.8 (8.6) *v* 10.3

Table 1 Patient characteristics

	Antifungal drug treatment					
	Fluconazole		Itraconazole		Total	
	n	%	n	%	n	%
Total number of patients	101	100.0	101	100.0	202	100.0
Male	63	62.4	57	56.4	120	59.4
Female	38	37.6	44	43.6	82	40.6
Age						
<45 years	37	36.6	28	27.7	65	32.2
45–60 years	43	42.6	54	53.5	97	48.0
>60 years	21	20.8	19	18.8	40	19.8
Diagnosis						
AML/ALL/CML	35	34.7	43	42.6	78	38.6
Lymphoma	37	36.6	36	35.6	73	36.1
Marrow aplasia	2	2.0			2	1.0
Multiple myeloma	21	20.8	20	19.8	41	20.3
Myelodysplasia	6	5.9	2	2.0	8	4.0
Autotransplantation						
Yes	60	59.4	55	54.5	115	56.9
No	41	40.6	46	45.5	87	43.1
Patient receiving GCSF						
Yes	42	41.6	43	42.6	85	42.1
No	59	58.4	58	57.4	117	57.9
Initial induction chemotherapy						
Yes	32	31.7	31	30.7	63	31.2
No	69	68.3	70	69.3	139	68.8
Neutropenic episodes in past year						
Yes	44	43.6	44	43.6	88	43.6
No	57	56.4	57	56.4	114	56.4
Duration of neutropenia, days (mean (SD)						
$<0.1\times10^9$/litre	11.8	(8.6)	10.3	(5.3)		
$<0.5\times10^9$/litre	15.2	(6.6)	15.1	(6.8)		

ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; CML, chronic myelocytic leukaemia; GCSF, granulocyte colony stimulating factor.

Table 2 Microbiologically documented infections

	Antifungal drug treatment		
	Fluconazole	Itraconazole	Total
Bacterial	**22**	**15**	**37**
Septicaemia	20	14	34
S aureus	1	0	1
Coagulase negative staphylococci	5	5	10
α and β haemolytic streptococci	10	5	15
S faecalis	2	1	3
S faecium	0	1	1
G morbilorum	1	0	1
Diphtheroid	1	1	2
E coli	0	1	1
Sinusitis			
P aeruginosa	0	1	1
Otitis externa			
P aeruginosa	1	0	1
Skin infection			
P acnes	1	0	1
Fungal	**4**	**4**	**8**
Pneumonia			
A fumigatus	1	4	5
Mucor species	1	0	1
Sinusitis			
A fumigatus	1	0	1
Mucor species	1	0	1

(5.3) days (mean (SD)), but the difference was not statistically significant.

MICROBIOLOGICALLY DOCUMENTED INFECTIONS

Proven bacterial septicaemia occurred in 20 patients treated with fluconazole and in 14 treated with itraconazole (table 2). Microbiologically documented bacterial infections other than septicaemia occurred in two patients in the fluconazole group (otitis externa; deep skin infection) and in one patient in the itraconazole group (maxillary sinusitis).

Proven systemic fungal infections occurred in four patients treated with fluconazole and in four treated with itraconazole. These eight infections included one case of mucormycosis in the sinuses, one in the lungs, two cases of *Aspergillus fumigatus* pneumonia in the fluconazole group, and four cases of *A fumigatus* pneumonia in the itraconazole group.

Table 3 Causes of death

	Antifungal drug treatment		
	Fluconazole	Itraconazole	Total
All deaths	7	11	18
Bacterial septicaemia	1	0	1
Proven *Aspergillus* infection	2	3	5
Proven *Mucor* infection	1	0	1
Suspected fungal infection	0	3	3
Non-infectious death	3	5	8

There were three patients with clinically apparent and culture documented oropharyngeal candidiasis in the fluconazole group and none in the itraconazole group. All these three cases were caused by *C albicans* and appeared during non-compliance.

None of these differences between the groups was statistically significant.

CLINICALLY DOCUMENTED INFECTIONS

Clinically documented bacterial infections occurred in 19 patients treated with fluconazole and in 12 treated with itraconazole. Most of these infections were in the lungs (17). Other sites of infection included the sinuses (6), skin (2), intravenous catheter entrance (2), mouth (1), vulva (1), rectum (1), and pericardium (1).

Clinically documented infections apparently caused by fungi occurred in seven patients in the fluconazole group and in four in the itraconazole group. All these infections were in the lungs.

There were no statistically significant differences between frequencies of suspected infection.

FEBRILE EPISODE OF UNKNOWN ORIGIN

In the fluconazole group, 14 patients developed FUO without documented infection. They all received antibacterial treatment and one of them proceeded to amphotericin. Of the patients on itraconazole, 29 received antibacterial treatment for simple fever and two of these proceeded to amphotericin. The difference in FUO between the groups was not statistically significant.

MORTALITY

Overall, seven patients in the fluconazole group died (6.9%) and 11 (10.9%) in the itraconazole group (table 3). This difference is not statistically significant. Death from proven bacterial infections occurred in one patient in the fluconazole group owing to ongoing septicaemia caused by coagulase negative staphylococci. Fungal disease caused death in three patients taking fluconazole and in six taking itraconazole. In the fluconazole group these three fungal deaths included two from *A fumigatus* pneumonia and one from sinusitis caused by *Mucor* spp.

In the itraconazole group there were three fatalities from *A fumigatus* pneumonia. The

other three were caused by clinically diagnosed fungal infection in the lungs.

There were three non-infectious deaths in the fluconazole group: encephalopathy (1), progressive disease (1), and tumour lysis syndrome (1). In the itraconazole group, five patients died from non-infectious causes. These were: progressive disease (2), encephalopathy (1), intractable heart failure (1), and intracerebral haemorrhage (1).

COMPLIANCE AND ADVERSE REACTIONS

Compliance was defined as good in 86% of the patients taking fluconazole and in 91% of those taking itraconazole. No major toxicity was seen. There were two rashes in the itraconazole group that were not attributable to causes other than itraconazole. In no patient was it necessary to stop the study drug because of adverse events.

USE OF INTRAVENOUS ANTIBACTERIAL AND ANTIFUNGAL AGENTS

In the fluconazole group, 64 patients received intravenous antibacterial treatment. Of these 64, 16 proceeded to amphotericin 9–26 days after developing fever. In the itraconazole group, 63 patients needed intravenous antibacterial treatment. Of these 63 patients, 13 received amphotericin, 8-28 days after becoming febrile. Thus, of all 202 patients in the study, 127 needed intravenous antibacterial treatment and 29 proceeded to amphotericin.

Kaplan–Meier plots for time to clinically suspected or proven fungal infection requiring amphotericin treatment showed almost superimposable curves, with identical median times to amphotericin of 16 days. Log rank testing showed no statistically significant differences.

FUNGAL ISOLATES IN SURVEILLANCE CULTURES

In the twice weekly mouth washes and the once weekly faecal samples, *Candida* spp were cultured quite often. At least two cultures were positive for the same *Candida* spp in 61 fluconazole recipients and in 54 itraconazole recipients. In the fluconazole group, *C albicans* was found at least twice in 28 patients, *C krusei* at least twice in 11, and *C glabrata* at least twice in 18.

Other *Candida* spp were found at least twice in four patients. In the itraconazole group these were *C albicans* (36 patients), *C krusei* (5), *C glabrata* (9), and other species (4).

PLASMA FLUCONAZOLE AND ITRACONAZOLE

The mean (SD) plasma fluconazole concentration was 2.56 (1.21) mg/litre in 319 samples. There were no differences between values in patients taken antacid drugs (ranitidine or omeprazole) and those whose gastric acid production was not inhibited.

The mean itraconazole + hydroxyitraconazole concentration was 1.04 (68) mg/litre, the ratio of hydroxyitraconazole/itraconazole being 2.09 (0.61). The combined hydroxyitraconazole + itraconazole concentration was lower in patients taken antacid drugs (0.81 (0.54)) than in patients taking no such compounds (1.13 (0.73)). The ratio of hydroxyitraconazole/itraconazole was not affected by the use of antacid drugs.

Discussion

In patients undergoing intensive chemotherapy with or without autologous stem cell grafting for haematological malignancies, our study showed that fluconazole or itraconazole appear to be equally effective for antifungal prophylaxis. There were no statistically significant differences between patients receiving 100 mg fluconazole or 200 mg itraconazole in the number of microbiologically documented systemic or superficial fungal infections nor in the use of empirical intravenous amphotericin. Small and statistically non-significant differences were noted in the frequency of clinically documented (pulmonary) fungal infections (in favour of itraconazole) and in mortality from fungal infection (in favour of fluconazole). The overall mortality of 8.9% in this study, and the mortality from microbiologically and clinically documented fungal disease of 4.5%, are well within the range of reported mortality data in similar patient groups.[21 22]

Fluconazole, in a large variety of dosages, has been associated with a very low incidence of both superficial and systemic candidiasis.[12–17] We chose the dose of 100 mg daily because, in a pilot study, we found 100 mg to be superior to 50 mg in terms of need for empirical amphotericin.[23] Furthermore, there is no hard evidence that higher doses are more effective and they are certainly more costly. Our frequency of microbiologically documented systemic fungal infection of 4% is similar to the rates described by Winston *et al* (4%) and Goodman *et al* (3%) using a daily dose of fluconazole of 400 mg.[12 13]

Although it has been suggested that the prophylactic use of fluconazole might lead to a selection of fluconazole resistant *Candida* spp like *C krusei* and *C glabrata* we, like others,[12 13 17 24] found no increase in systemic or superficial infection caused by *C krusei* or *C glabrata*.

Theoretically, intraconazole could be a more appropriate drug for prevention of fungal disease in neutropenic patients because of its activity against *Aspergillus* spp. However, randomised trials examining the efficacy of itraconazole in this particular setting are scarce and not conclusive.[20] We chose a dose of 200 mg daily, according to the manufacturer's guidelines for preventive use. We were able to show absorption of the drug in every patient assigned to intraconazole.

The plasma trough levels of itraconazole that we found are well within the published range and almost equal to the MIC breakpoint for itraconazole in candidal disease, as recently proposed by Rex *et al*.[25] Itraconazole in the dose used proved clinically effective in preventing mucosal candidal disease.

There are no data available on whether such a plasma concentration represents an effective level for preventing aspergillosis. It has been suggested that a recently available oral solution would result in better absorption and thereby in increased efficacy. Steady state levels of itraconazole using daily doses of 200 mg of the oral solution are between 1.0 and 2.0 mg/ml of plasma.[26 27] However a randomised trial,

published in abstract, comparing oral solutions of itraconazole (2.5 mg/kg) *v* fluconazole (100 mg) once daily in a similar patient group also showed that both drugs were effective prophylactic antifungal agents, with no major differences in efficacy.[28] The dose of itraconazole used in that study (2.5 mg/kg) is comparable with that used in our study (200 mg).

In both the fluconazole and the itraconazole recipients, the percentage of patients proceeding to intravenous amphotericin was remarkably low (16% and 13%, respectively). This rate is lower than reported by Winston *et al* and Goodman *et al*, using higher doses of fluconazole as prophylaxis,[12 13] and even lower than in the study by Menichetti *et al*, who examined the effect of 150 mg of fluconazole.[17] It would be an overinterpretation of our results to claim that the prophylactic use of antifungal treatment was solely responsible for the low rate of systemic antifungal therapy used in our study. Since much amphotericin use is empirical, one factor that contributed to this low rate could have been the effective and strictly applied antibacterial preventive and therapeutic regimen used in our study. The prophylactic use of a quinolone effectively prevented almost all Gram negative infections, as found in other studies (for instance, Bow *et al*[29]). In an earlier study, we found imipenem-cilastatin to be an effective antibiotic in febrile neutropenic patients, a conclusion also reached in a meta-analysis of the use of this antibiotic in neutropenia and fever.[30 31]

Compliance was good for both drugs, and no clinically important side effects were attributed to the use of either of them.

CONCLUSIONS

Fluconazole is as effective as itraconazole in preventing systemic and superficial fungal infection and the empirical use of amphotericin in neutropenic patients. Fluconazole is the preferred drug because of the smaller number of capsules needed to deliver the dose used in the study. Furthermore, there is no need to consider time intervals between meals and drug ingestion when using fluconazole. This study shows that in patients treated for haematological malignancies with or without autologous stem cell transplantation, fluconazole at a dose of 100 mg daily results in a low frequency of fungal disease.

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