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The efficacy of itraconazole against systemic fungal infections in neutropenic patients: a randomised comparative study with amphotericin B

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Summary

In a randomised clinical trial, we compared the efficacy of the new triazole drug itraconazole (200 mg orally twice daily) with that of amphotericin B (0.6 mg/kg daily or 0.3 mg/kg in combination with flucytosine) in neutropenic ($< 500 \times 10^6/l$ neutrophils) patients with proven or highly suspected systemic fungal infections. Patients with unexplained fever alone were not included in the study. Of the 40 patients enrolled, 32 patients (16 males, 16 females) were evaluable. Sixteen patients (median age 49 years) were treated with itraconazole for a median period of 20 days and 16 patients (median age 32 years) received amphotericin B for a median period of 13 days. The overall clinical response was 10/16 (63%) for patients treated with itraconazole and 9/16 (56%) for patients treated with amphotericin B ($P > 0.90$). Itraconazole seemed to be more effective against *Aspergillus* infections, whereas amphotericin B seemed to be more effective against candidal infections, although the differences were not statistically significant.

Introduction

Systemic fungal infections continue to be a major threat to neutropenic patients, the most important causative agents being species of *Candida* and *Aspergillus*.¹ The standard therapy for these infections is amphotericin B or a combination of amphotericin B and flucytosine in case of candidal infections.² Because the diagnosis of fungal infections is often established only at post-mortem examination, many physicians administer empirical antifungal therapy to neutropenic patients with unexplained fever who do not respond to broad-spectrum antibacterial treatment.^{3,4} Treatment with these antifungal drugs, however, is often disappointing in neutropenic patients⁵ and may be associated with considerable side-effects. Therefore, more effective and less toxic antifungal drugs are needed. Itraconazole is a new triazole antifungal drug with activity against *Candida* and *Aspergillus* species both *in vitro* and in experimental animal infections.⁶⁻⁹ Deep-seated candidal infections and

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invasive aspergillosis have been treated effectively with itraconazole without apparent toxicity in non-neutropenic patients^{10,11} and, more recently, also in small numbers of neutropenic patients^{12,13} and in a patient with chronic granulomatous disease.¹⁴ Because of its low degree of toxicity, the possibility of prolonged oral treatment with itraconazole could prove to be an important advantage over amphotericin B. Therefore, we conducted a prospective, randomised clinical trial in order to compare the efficacies of itraconazole and amphotericin B in neutropenic patients with proven or highly suspected systemic fungal infections.

Materials and methods

Patients and definitions

Three hospitals, the Nijmegen University Hospital, the Leiden University Hospital and the Leyenburg Hospital of The Hague, took part in the study. All neutropenic patients with proven or suspected fungal infections were considered eligible for the study. Neutropenia was defined as fewer than $500 \times 10^6/l$ neutrophils in the peripheral blood. The patients were nursed in protective isolation and received oral non-absorbable antimicrobial drugs, including amphotericin B, for selective decontamination of the gastrointestinal tract.¹⁵ Fungal infection was considered to be definite if fungi were cultured from deep tissues or sterile body fluids or were identified at these sites by cytological or histological examination. In the case of candidaemia, at least two blood cultures taken by venupuncture from different sites had to be positive with the same species. Because systemic fungal infections are often difficult to prove in neutropenic patients we also included patients with highly suspected fungal infection, i.e. those with a clinical site of infection without a known bacterial or viral causative agent. In the case of a pulmonary infiltrate without histological proof of deep tissue involvement, fungal infection was considered to be probable when *Aspergillus* species were isolated from the sputum and possible when *Candida* species were isolated. The distinction between *Candida* and *Aspergillus* was made because of the frequent isolation of *Candida* species from the skin and mucous membranes of neutropenic patients without signs of infection, whereas the isolation of *Aspergillus* species from the sputum of a neutropenic patient is considered to be highly indicative of the presence of this infection.¹⁶ Patients with unexplained fever as a single sign were excluded from the study. Patients unable to take oral medication were also excluded, as were patients who had to take H₂-receptor antagonists which may interfere with the absorption of itraconazole from the gastrointestinal tract.¹⁷

A patient was presumed to have responded to therapy when there was at least a 50% decrease in the size of the initial site or the severity of the infection or when all signs of infection had disappeared. If the fungal infection persisted or progressed, therapy was considered to have failed. If a patient had to discontinue treatment with itraconazole because of problems in swallowing oral medication, therapy was also considered a failure.

Drug regimens

Amphotericin B for intravenous use (Fungizone[®], E. R. Squibb & Sons) and flucytosine (Ancotil[®], Hoffmann LaRoche) were purchased from their respective manufacturers; itraconazole was provided by Janssen Pharmaceuticals, Beerse, Belgium, in capsules containing 50 mg of the drug in polyethylene glycol. The study was approved by the ethical committees of the participating hospitals. After informed consent was obtained, each patient was randomised so as to receive either itraconazole or amphotericin B. The decision to combine amphotericin B with flucytosine for a candidal infection was made by the attending physician. After a test dose of 1 mg, the dose of amphotericin B was rapidly increased to 0.6 mg/kg intravenously daily. When administered in combination with flucytosine (150 mg/kg daily), the dose of amphotericin B was lower (0.3 mg/kg). Itraconazole was administered orally at a dose of 200 mg every 12 h after a meal. When a patient was given itraconazole, oral amphotericin B for fungal prophylaxis was discontinued because of possible antagonism between azole drugs and amphotericin B.¹⁸

Laboratory evaluation

Blood counts, serum electrolytes, serum creatinine and liver enzymes were determined before antifungal treatment was started and twice weekly thereafter in order to monitor renal and hepatic toxicity and to assess bone marrow recovery. Renal toxicity was defined as an increase in serum creatinine of at least 30%, hepatic toxicity was defined as an increase in serum glutamic oxaloacetic transaminase (SGOT) or serum alkaline phosphatase of at least 30% of the initial value obtained before treatment was started.

Statistical analysis

The χ^2 test with the Yates-correction was used in order to compare the results of the two treatment groups.

Results

Of the 40 patients who entered the study, 32 were evaluable. Five patients should not have been included because of their not having any clinical site of infection. Three other patients were also excluded from further evaluation: one died only a few hours after therapy began and one proved to have bacterial pneumonia, while treatment with itraconazole had to be discontinued in another because of a rash.

Patient characteristics

Of the 32 evaluable patients, 16 were treated with itraconazole and 16 received amphotericin B; five of those treated with amphotericin B also received flucytosine. The patient characteristics were similar within the two treatment groups except for a higher median age for the patient treated with itraconazole (Table I). The most common underlying condition was acute leukaemia, 63% all patients being severely neutropenic ($< 100 \times 10^6/l$ neutrophils) at the time antifungal therapy began, either due to their disease or as a result of the cytostatic treatment.

Table I Characteristics of 32 patients with suspected or proved fungal infections

Characteristic	Patients treated with	
	Amphotericin B*	Itraconazole
Number of patients	16	16
Number of males	7	9
Number of females	9	7
Median age (years)	32	51
Age range (years)	19-51	15-74
Median duration of neutropenia before treatment (days)	11	10
Number of patients with:		
Leukaemia	14 (88%)	13 (81%)
Lymphoma	1 (6%)	2 (13%)
Others†	1 (6%)	1 (6%)
Number of patients with neutrophils < 100 × 10 ⁶ /l	11 (69%)	9 (56%)

* Five patients received amphotericin B combined with flucytosine.

† One patient with aplastic anaemia treated with amphotericin B and one patient with multiple myeloma treated with itraconazole.

Fungal infections

Fungal infection was definite in seven, probable in 11 and possible in 14 cases. The causative agent was *Candida* in 16 cases (*Candida albicans*: 15 patients; *Candida* sp.: one patient) and *Aspergillus* in 13 cases (*Aspergillus fumigatus*: seven patients; *A. niger*: one patient; *A. flavus*: one patient; *Aspergillus* spp.: four patients). In three patients with possible fungal infection, a causative agent could not be identified. The most common site of infection was the lung, pulmonary infiltrates being present in 27 of the 32 patients. One patient treated with itraconazole had both pulmonary and paranasal aspergillosis, whereas one patient receiving amphotericin B had combined pulmonary and cerebral aspergillosis. In addition, two patients treated with itraconazole had candidaemia, whereas two patients receiving amphotericin B had oesophagitis and one had endophthalmitis.

Clinical efficacy

The median duration of treatment was 20 days (range 1-104 days) for patients treated with itraconazole and 13 days (range 7-57 days) for those receiving amphotericin B. The median cumulative dose of amphotericin B administered was 318 mg (range 166-1560 mg). Concomitant antibiotic therapy was administered to 13 patients on itraconazole and 11 patients on amphotericin B. The overall response to treatment is shown in Table II. Ten of 16 patients (63%) treated with itraconazole and nine of 16 patients (56%) receiving amphotericin B responded to treatment ($P > 0.90$). Three patients received itraconazole for less than 3 days because of an inability to swallow oral

Table II Clinical outcome of 32 patients with suspected or proved fungal infections

Fungal infection	Patients treated with			
	Amphotericin B*		Itraconazole	
	Number of patients	Number responding	Number of patients	Number responding
Candidiasis				
Definite	1	0	3	0
Probable	1	1	—	—
Possible	8	6	3	2
Aspergillosis				
Definite	2	0	1	1
Probable	3	2	7	5
Unknown	1	0	2	2
Total	16	9	16	10

* Five patients received amphotericin B combined with flucytosine.

medication. When these patients are excluded, the overall response to treatment with itraconazole was 77%. When definite and probable infections are taken together, six of 11 patients treated with itraconazole and three of seven patients receiving amphotericin B responded to treatment ($P > 0.90$). Two of six patients with *Candida* infections treated with itraconazole and seven of 10 patients receiving amphotericin B responded to treatment. Six of eight patients with *Aspergillus* infections treated with itraconazole and two of five patients receiving amphotericin B responded also.

Overall, 13 of 15 patients with neutrophil recovery ($> 500 \times 10^6/l$) during treatment and only six of 17 patients without neutrophil recovery responded to treatment ($P < 0.01$). Although this trend was apparent for patients receiving itraconazole as well as amphotericin B, the numbers within the treatment groups were too small to reach statistical significance.

Four patients treated with itraconazole and six having amphotericin B died during the period of treatment or shortly (< 3 days) thereafter; autopsy findings were available for seven of these patients. For patients receiving itraconazole, the causes of death were cerebral haemorrhage (one patient), interstitial pneumonitis (one patient), polymicrobial septicaemia (including candidaemia) (one patient) and pulmonary candidiasis (one patient). For patients treated with amphotericin B the causes of death were *Pseudomonas* septicaemia (one patient), interstitial pneumonitis (two patients) and invasive aspergillosis (three patients).

Itraconazole plasma concentrations

Blood samples were drawn from eight patients 3 h after oral administration of 200 mg itraconazole for determination of the plasma concentration by high-pressure liquid chromatography (Janssen Pharmaceuticals, Beerse, Belgium).

Table III Renal and hepatic toxicity

Laboratory test	Findings in 20 patients with abnormal* values during treatment with	
	Amphotericin B† (20 patients)	Itraconazole (20 patients)
Serum creatinine	6 (30%)	3 (15%)
Serum alkaline phosphatase	5 (25%)	2 (10%)
SGOT	11 (55%)	8 (40%)

* > 30% increase in pretreatment values.

† Five patients received amphotericin B combined with flucytosine.

SGOT = serum oxaloacetic transamiase.

The plasma concentration varied between 192 and 2045 ng/ml for five patients who responded to treatment and between 16 and 666 ng/ml for three patients who did not respond to treatment.

Side effects

Fever and chills were seen in five of 20 patients treated with amphotericin B despite premedication with pethidine. In one case, treatment with itraconazole had to be discontinued because of the appearance of a generalised rash shortly after administration of the drug on two consecutive occasions. Laboratory evaluation revealed renal toxicity in six of 20 patients treated with amphotericin B and three of 20 patients treated with itraconazole ($P = 0.45$; Table III). Renal toxicity contributed to the death of one patient on amphotericin B and necessitated discontinuation of the drug in another. Nephrotoxicity was reversible in two patients receiving itraconazole despite continuation of the drug and was probably related to shock in a third case. There was no difference in the incidence of hepatotoxicity (Table III).

Discussion

In the present study, we found no significant difference between the efficacies of itraconazole and amphotericin B against systemic fungal infections in neutropenic patients. Even so, we recognise the fact that the number of patients in the study was too small so as to fully exclude superiority of one of the two drugs.

A large proportion (41%) of the fungal infections was caused by *Aspergillus* spp., whereas in most studies over 80% of the fungal infections are caused by species of *Candida*.¹⁹ The explanation for this difference may be two-fold. First, in order to be able to discriminate between infection and colonisation, the criteria for candidal infections were stricter than those for *Aspergillus* infections. Secondly, the relative frequency of *Aspergillus* infections compared to candidal infections may have been enhanced by the use of non-absorbable antimicrobial drugs, including oral and local amphotericin B, for preventing infection in our patients.¹⁵ This regimen, in combination with the restricted

use of broad-spectrum antibiotics, has proved to be effective in the prevention of Gram-negative and candidal infections but is less effective as prophylaxis against *Aspergillus* infections. Despite the grave prognosis for *Aspergillus* infections in neutropenic patients, the efficacy of itraconazole against these infections was favourable in our study since six of eight patients responded to treatment. None of the patients given itraconazole died of aspergillosis, whereas three patients treated with amphotericin B died of invasive aspergillosis. Itraconazole seemed somewhat less effective than amphotericin B against candidal infections, although the difference was not statistically significant. Moreover, two patients who failed to respond to itraconazole, but none of the patients treated with amphotericin B, had candidaemia.

The daily dose of amphotericin B used in our study (maximal 0.6 mg/kg) was lower than that recommended by some authors and the duration of treatment was rather short. Even so, there is no general agreement on the daily dose of amphotericin B that should be administered to neutropenic patients with systemic fungal infections and the doses used in this study agree with the recommendations made.²⁰ The median duration of treatment of fungal infections in neutropenic patients is determined by the complicated course in this group of patients and was comparable to the duration of treatment reported.¹⁹

At the time of this study, the most important limitation on the use of itraconazole was the absence of an intravenous form of the drug and the variable absorption after oral administration in patients with gastro-intestinal disturbances. Indeed, plasma concentrations of itraconazole tended to be lower in patients who did not respond to treatment compared to patients who did respond to treatment. Plasma concentrations were not obtained for three other patients who had to discontinue treatment with itraconazole within 3 days because of difficulties in swallowing the drug; presumably, their plasma concentrations were very low. Although the antifungal efficacy of itraconazole is difficult to evaluate in these patients, we included them as failures in the evaluation of the response to treatment because we wanted to compare the usefulness of the two drugs in the situation in which systemic fungal infections arise.

Only very recently has an intravenous form of itraconazole been developed. It is now being evaluated for safety in volunteers (G. Cauwenbergh, personal communication). All being well, this new form of itraconazole should result in a major improvement in the application of the drug in patients with inadequate absorption.

Although our study was designed as a conventional clinical trial of efficacy, a more appropriate approach may be to try to establish equivalence between the two treatments.²¹ If this were to be the case, itraconazole should be preferred to amphotericin B because it is less toxic and because of the possibility of prolonged oral treatment for outpatients.

In conclusion, the present study indicates that itraconazole may be a useful new drug against systemic fungal infections in neutropenic patients. Larger studies, preferably with an intravenous form of itraconazole, are necessary in order, hopefully, to establish more firmly the efficacy of itraconazole compared to that of amphotericin B.

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