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Oral Prophylaxis with Miconazole or Ketoconazole of Invasive Fungal Disease in Neutropenic Cancer Patients*

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Abstract—*Ketoconazole or miconazole was randomly administered to 42 and 46 neutropenic patients respectively. Of the total number of stool cultures 12% were positive for yeasts in both groups; 4% of the total number of cultures from other sites (nose, throat, skin) were positive in both groups.* Candida albicans *was the most common isolate, but other fungal species were also identified. No patient developed fungemia; 5/88 patients developed severe oropharyngeal candidiasis while receiving prophylaxis. Among the 21 autopsies performed, 5 cases of pulmonary aspergillosis and 2 local and 1 disseminated candidiasis were demonstrated in 7 patients. Although there was no placebo group of patients in this study, post-mortem data suggest that miconazole or ketoconazole might reduce the incidence of disseminated candidiasis in neutropenic patients.*

INTRODUCTION

INVASIVE fungal diseases remain a major cause of morbidity and mortality in cancer patients and particularly in neutropenic patients [1–3]. Disseminated candidiasis and aspergillosis are the most common fungal infections demonstrable at autopsy in neutropenic cancer patients. Overall, several reviews obtained from various cancer centers have reported that 30–50% of leukemics patients have evidence of invasive fungal infections at autopsy. Early diagnosis of deep-seated fungal infection is difficult and optimal therapy remains to be defined as the mortality is still elevated despite amphotericin B administration. Therefore, prevention of invasive fungal disease may represent a valuable approach in these debilitated patients.

The aim of this study is to evaluate the effectiveness of miconazole and ketoconazole when administered prophylactically in neutropenic cancer patients. These antifungal agents are imidazole derivatives that can be given orally. Miconazole is partially absorbed, with an oral bioavailability of about 25–30%, while ketoconazole administration results in significant gastrointestinal absorption. Ketoconazole is the latest described imidazole and has already shown promising effects in chronic mucocutaneous candidiasis [4].

MATERIALS AND METHODS

From 1 October 1979 to 31 October 1980, 88 adult neutropenic patients (<1000 neutrophils/μl) were randomly allocated to receive miconazole or ketoconazole. Both drugs were administered with a meal as 250 mg of miconazole every 6 hr or 200 mg of ketoconazole once a day. All patients were hospitalized at the Institut Jules Bordet, the cancer center of Brussels University. Leukemic patients and those who received an autologous bone marrow transplant were included in this study at the time of initiation of intensive chemotherapy. At randomization, patients were free from infection and not receiving antibiotics. The patients were also randomly assigned to receive cotrimoxazole or a placebo, in order to evaluate the role of cotrimoxazole as an antimicrobial prophylaxis (EORTC protocol). Data on bacterial infections in these patients will be reported separately. All patients received a cooked food diet. Six patients in both groups were isolated in a laminar air flow room while all the other patients were hospitalized in single rooms with reverse isolation. The

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prophylactic regimens were discontinued when the neutrophil count was restored to >1000 polymorphonuclears/μl. The patients who did not remain neutropenic for at least 7 days were excluded. All patients had surveillance cultures taken at the time of randomization and twice weekly thereafter. The sites investigated routinely were nose, ears, pharynx, axillae, urine and stools. Samples from other sites were obtained for culture depending on clinical findings. Blood cultures were obtained when the temperature was higher than 38.5°C. Microbiological identification of all morphologically distinct isolates was performed. Semi-quantitative cultures were performed on stools; the minimal colony quantitation was 10^3CFU/g. Evaluation of possible infection was obtained at each fever peak (<38.5°C) and included 3 blood cultures, urine analysis and cultures of nose, pharynx and stools, as well as a chest X-ray, fundoscopic examination of both eyes and fungal serology. Invasive procedures, such as biopsies and cultures of liver, bone marrow and skin, were performed in some patients when indicated and feasible. Empirical therapy with broad spectrum antibiotics was initiated immediately after the fever work-up. If the patients remained febrile depite this empiric therapy, administration of intravenous amphotericin B was started after 4 days. All autopsies were reviewed by one of the investigators (F.MC). Invasive fungal disease was defined as histological demonstration of fungi, mycelia, yeasts and/or pseudohyphae in tissues.

RESULTS

A total of 88 patients were evaluated: 46 patients were randomly allocated to receive miconazole and 42 patients were assigned to receive ketoconazole. The underlying diseases of the patient are indicated in Table 1. The majority had acute leukemia, lymphoma or small cell carcinoma of the lung, the latter being treated with intensive chemotherapy and autologous bone marrow transplantation. The age and sex distribution of the patient was similar for both groups. The mean age was 54.5 yr in the miconazole group and 53.0 yr in the ketoconazole group. The mean duration of prophylaxis was 27 days in both groups of patients and the mean duration of severe neutropenia (defined as a polymorphonuclear count <500 per μl) was 15.5 days and 18.4 days for the miconazole and ketoconazole groups respectively.

Table 1. Underlying disease

	No. of patients	
	Miconazole ($n=46$)	Ketoconazole ($n=42$)
Acute leukemia	20	22
Lymphoma	1	8
Lung cancer*	12	7
Ovarian cancer	-	2
Breast cancer	7	-
Head and neck cancer	4	1
Myelofibrosis	-	1
CML	1	1
Aplastic anemia	1	-

*Patients with small cell carcinoma treated with intensive chemotherapy and autologous bone marrow transplantation.

The distribution of patients among the cotrimoxazole and the placebo groups were also similar. Oral cotrimoxazole was administered prophylactically to 26 and 25 patients respectively in the miconazole and ketoconazole groups, while the placebo was administered to 20 patients in the miconazole group and 17 patients in the ketoconazole group. Febrile neutropenic patients received empirical broad spectrum antibiotics; a comparable number of patients in both groups were treated with systemic antibiotics. Overall, 26 patients in the miconazole group and 29 patients in the ketoconazole group had febrile episodes requiring the initiation of systemic antibiotic therapy.

The incidence of positive surveillance cultures is reported in Table 2. No difference could be observed between the patients receiving miconazole or ketoconazole. About 30% of the patients in both groups had positive surveillance cultures, either from stool specimens or from other sites. The total number of samples evaluated were comparable in both groups. Among the stool cultures 12% were positive for fungi in both groups of patients, while 4.2 and 3.4% respectively of the cultures obtained from other sites were positive for fungi in the miconazole and the ketoconazole groups. Among 7 and 3 patients receiving miconazole or ketoconazole who had yeasts in the initial stool surveillance cultures, 3 and 2 respectively showed subsequent eradication of the organisms. The recovery of fungal organisms in the surveillance cultures was analysed according to whether the patients did or did not receive oral antibiotic prophylaxis. As

Table 2. Surveillance cultures

	Miconazole	Ketoconazole
Total stool cultures	295	284
Positive cultures for fungus	36 (12.2%)	36 (12.6%)
No. of patients with positive culture (at least 1)	15 (32.6%)	14 (33.3%)
Total cultures from other sites	954	842
Positive cultures for fungus	41 (4.2%)	29 (3.4%)
No. of patients with positive culture (at least 1)	18 (39.1%)	14 (33.3%)

indicated in Table 3, approximately 9% of the stool cultures were positive among the patients who did not receive oral antibiotic prophylaxis, while 15% of the stool cultures from patients receiving cotrimoxazole were positive for a fungus. However, this difference is not statistically significant. Positive stool cultures were obtained in 7/20 and 3/17 patients respectively in the miconazole and ketoconazole groups of patients who had not received cotrimoxazole, while 8/26 and 11/25 patients respectively receiving it in addition to the antifungal regimen had positive surveillance stool cultures for fungi; 11/25 patients (44%) receiving concomitant cotrimoxazole and ketoconazole had positive stool cultures for fungi, but only 3/17 patients (17.6%) receiving ketoconazole alone had positive cultures. However, this difference was not statistically significant. The mean log number of viable yeast organisms in the stools (± standard deviation) was 3.83 ± 1 for the patients receiving ketoconazole and 4.5 ± 1.3 for the patients receiving miconazole. *Candida albicans* was the most commonly yeast isolated in the surveillance cultures, but other species such as *Candida krusei, C. parapsilosis* and *Torulopsis glabrata* were also identified. True colonization of the gastrointestinal tract (i.e. appearance of the same organism in 2 or more consecutive stool cultures) was observed in 7 patients receiving miconazole and in 8 patients receiving ketoconazole. *Candida albicans* was found to be the colonizing yeast in 5 patients in both groups and colonization by *T. glabrata* occurred in 2 patients in each group. One patient receiving ketoconazole was colonized by *C. krusei*. Colonization by fungi of other sites (nose, throat, sputum etc.) was observed in 7 patients receiving miconazole and in 5 patients receiving ketoconazole.

Table 3. *Surveillance cultures: relationship to concomitant therapy with cotrimoxazole*

	Miconazole	Ketoconazole
No cotrimoxazole		
Stool culture		
Percentage of positive cultures for fungus	9.4	8.4
No. of patients with positive culture (at least 1)	7 (35.0%)	3 (17.6%)
Other sites		
Percentage of cultures for fungus	4.9%	2.3%
No. of patients with positive culture (at least 1)	8 (40.0%)	4 (23.5%)
Cotrimoxazole		
Stool culture		
Percentage of positive cultures for fungus	14.9	15.2
No. of patients with positive culture (at least 1)	8 (30.7%)	11 (44.0%)
Other sites		
Percentage of positive cultures for fungus	3.7	4.2
No. of patients with positive culture (at least 1)	10 (38.4%)	10 (40.0%)

Four patients had surveillance cultures from nose or sputum positive for *Aspergillus* spp. while receiving miconazole or ketoconazole. Among the 3 patients in the miconazole group, 2 had autopsy-proven invasive aspergillosis. The only patient in the ketoconazole group who had a positive surveillance culture (from the nose) also had histological evidence of invasive pulmonary aspergillosis at autopsy. Two other patients receiving ketoconazole also had autopsy-proven pulmonary aspergillosis, but in the absence of positive surveillance cultures.

Among the 46 patients who received miconazole 14 were treated with amphotericin B for suspected or microbiologically documented fungal infections. In the ketoconazole group 10/42 patients were treated similarly with amphotericin B. The systemic antifungal therapy was initiated after a mean duration of 30 days and 21 days of prophylactical administration of miconazole or ketoconazole respectively. These 24 patients who were treated with amphotericin B should be considered to be at higher risk of developing fungal infection since the mean duration of severe neutropenia observed in these patients was 28 days and 25 days respectively, while the overall mean duration of PMM $<500/\mu l$ was 15 and 18 days in the miconazole and ketoconazole groups. Moreover, fungal colonization of the gastrointestinal tract and/or other sites was documented in 9/14 and 7/10 patients receiving miconazole and ketoconazole before the administration of amphotericin B for suspected or proven fungal infection. As mentioned in Table 4, no difference between the 2 groups of patients could be determined. The mortality rate was similar for both groups; among the 12 autopsies available, 3/7 indicated an invasive fungal infection in the miconazole group and 4/5 in the ketoconazole group. The mean total dose of amphotericin B received by the patients with autopsy-proven fungal infection was 475 mg ± 236, while the

Table 4. *Antifungal therapy*

	Miconazole ($n = 46$)	Ketoconazole ($n = 42$)
No. of patients treated with amphotericin B	14	10
Death while on amphotericin B	10	8
No. of autopsies	7	5
No. of patients with autopsy-proven fungal disease	3	4

mean total dose received by the patients with autopsy negative for a deep-seated fungal infection was 550 mg ± 320.

Table 5 shows the autopsy findings of these patients. The overall mortality was similar in both groups of patients, as well as the number of autopsies. Among the 88 patients evaluated in this study 7 had evidence of invasive fungal infection at autopsy, 6 of them having been treated with amphotericin B prior to death. Pulmonary aspergillosis was the most frequently identified fungal infection: 2 in the miconazole and 3 in the ketoconazole group. Overall, 3 invasive candidiases were observed, 1 localized to the gastric wall of a patient receiving miconazole prophylactically; the 2 others occurred in patients receiving ketoconazole: one of them had extensive oesophageal candidiasis demonstrated at autopsy and the other had disseminated candidiasis (*Candida albicans*) involving the skin and the myocardium.

In addition to the autopsy findings, which are the most reliable in demonstrating fungal infection, the incidence of oropharyngeal candidiasis was also evaluated. Among the patients who received miconazole, 2/46 developed severe symptoms, clinical signs and positive cultures from oral lesions. Infection developed in one patient on day 15 of the prophylactic regimen; *Candida albicans* was isolated from the thrush lesions and the patient had a favorable outcome after nystatin therapy. The other patient developed mucosal lesions after 36 days on miconazole; *Candida pseudotropicalis* was isolated but the patient responded poorly to nystatin and was treated successfully with intravenous amphotericin B. Three patients developed oral candidiasis while receiving ketoconazole prophylactically: *Candida albicans* was the organism isolated from all 3 patients, on days 10, 22 and 22 respectively. These 3 patients were treated with intravenous amphotericin B: one had a favorable outcome, one died and had autopsy-proven disseminated candidiasis and the third patient died with an autopsy-proven pulmonary aspergillosis but without evidence of persistent candidiasis.

Table 5. Mortality

	No. of patients	
	Miconazole ($n = 46$)	Ketoconazole ($n = 42$)
Overall mortality	15	16
Autopsy	11	10
Number of patients with fungal disease (at autopsy)	3/11	4/10
Pulmonary aspergillosis	2	3*
Invasive candidiasis	1 (local)	1 (disseminated) 1 (local)

*One patient had pulmonary aspergillosis and local invasive candidiasis.

As far as tolerance is concerned, 7/46 (15.2%) of the patients receiving miconazole discontinued their treatment because of severe gastrointestinal side-effects, while 3/42 (7.1%) in the ketoconazole group developed severe intolerance. The administration of the prophylactic regimen was discontinued after a mean duration of 6.1 and 17.3 days respectively. However, all these patients were treated with other medications (such as cotrimoxazole, gentamicin, allopurinol and antineoplastic chemotherapy) and it is difficult to establish the specific role of the antifungal agents as the cause of the patients' refusal to continue the prophylactic administration of miconazole or ketoconazole. Moderate intolerance which did not interfere with the intake of the antifungal drugs did occur in 4 patients (8.6%) in the miconazole group and in 3 patients (7.1%) in the ketoconazole group. Altered liver function tests, unexplained otherwise, were observed in one patient receiving miconazole and in 2 patients receiving ketoconazole.

DISCUSSION

Invasive fungal infection is a serious complication in neutropenic cancer patients. These infections are often fatal. Although early diagnosis is difficult, prompt initiation of therapy may improve the outcome of these patients [5]. Another approach is to prevent the colonization, and subsequent invasion and dissemination by fungal organisms, with a prophylactic regimen aimed at decreasing the number of yeasts within the gastrointestinal tract. It is recognized that gastrointestinal antifungal prophylaxis would not prevent infection by airborne fungal pathogens such as *Aspergillus* spp.

Nystatin has been used, at various dosages, without definite evidence of effectiveness. In a recent review of fungemia, approximately 30% of cancer patients who had *Candida albicans* fungemia were receiving nystatin prophylactically when they developed fungemia [6]. Oral amphotericin B has also been evaluated to prevent the incidence of candidiasis in patients with hematological malignancies [7]. In this double-blind study Edzinli *et al.* compared the outcome of patients receiving 200 mg of oral amphotericin B to a similar group of patients receiving a placebo. Eight out of 33 patients who received the placebo and 2/29 who received amphotericin B had histological evidence of disseminated candidiasis. Miconazole and ketoconazole are mainly active on yeast organisms; these agents are fungistatic but

occasionally a fungicidal effect has been observed. Encouraging studies have been published, particularly for chronic mucocutaneous candidiasis [4]. However, there is no definite data yet indicating the role of the imidazoles in the management of disseminated fungal infection, particularly among compromised patients [8].

The present study evaluated the role of these agents in patients with leukemia and patients with small cell carcinoma of the lung undergoing intensive chemotherapy with autologous bone marrow transplantation. The surveillance cultures revealed a comparable rate of colonization among the patients receiving miconazole or ketoconazole. Approximately 30% of these patients had positive stool cultures for yeast organisms. Approximately 4% of the surveillance cultures obtained from other sites than stools (nose, throat, urine, skin) were positive for a fungus. Fungal surveillance cultures are a valid method of evaluating the risk of disseminated *Candida* infection in highly susceptible patients [9–12]. Whether patients in the miconazole or ketoconazole groups did or did not receive cotrimoxazole did not change the incidence of positive surveillance cultures for fungi.

The overall evaluation of antifungal prophylaxis should be based on autopsy findings. In that respect there was no difference here between miconazole or ketoconazole. Among the 88 patients entered in this study 21 were autopsied, of which 7 (30% of the autopsied patients, 8% of all the patients entered) had histological evidence of invasive fungal infection. Pulmonary aspergillosis was the most common infection and was found in 5/7 patients. There were 3 cases of invasive candidiasis demonstrated by autopsy, one in the group of patients receiving miconazole and 2 in the group of patients receiving ketoconazole. Only one patient had autopsy-proven disseminated candidiasis. All these autopsy-proven invasive fungal infections were observed in leukemic patients, with the exception of one patient with candidiasis located in the gastric wall who had small cell carcinoma of the lung. Despite the fact that the overall incidence of positive surveillance cultures was unaffected by cotrimoxazole absorption, it is worthwhile to mention that among the 7 patients who had autopsy-proven invasive fungal infection 6 patients had been treated prophylactically with cotrimoxazole. Although there was no placebo group in the present study the incidence of disseminated candidiasis was remarkably low, as only one out of 88 patients has histological evidence of disseminated candidiasis; two other patients had invasive candidiasis localized to the gastrointestinal tract. Edzinli *et al.* found 8/33 disseminated *Candida* infections in comparable patients receiving no antifungal prophylaxis [7]. It should also be stressed that none of our 88 patients developed fungemia. These observations might indicate some value of the imidazoles to prevent locally invasive as well as disseminated candidiasis in neutropenic patients. However, the high rate of pulmonary aspergillosis identified in this series must be underlined. It is interesting to note also that among 6 patients who failed on amphotericin B therapy 4 were still receiving the oral imidazole, while prophylaxis with miconazole or ketoconazole had been discontinued in 5/6 patients who also were treated with intravenous amphotericin B and did not have evidence of fungal infection at autopsy. These numbers are too small to make any final statement, but further evaluation of a possible antagonism between the imidazoles and amphotericin B is warranted [13].

Alterations of the enzymatic liver tests and rare cases of hepatitis have been reported [14]. Although the complex underlying diseases and the multiple drug therapy administered to our patients make the evaluation of the individual toxicity difficult, 1/46 patients receiving miconazole and 2/42 patients receiving ketoconazole showed alterations of the liver function tests. Discontinuation of miconazole and ketoconazole for severe intolerance occurred in 7 and 3 patients respectively.

To conclude, our study suggests a possible effectiveness of orally administered miconazole or ketoconazole for the prevention of disseminated *Candida* infection in neutropenic patients. This study is now being repeated using placebo and oral amphotericin B for comparison.

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