A double-blind comparison of itraconazole and fluconazole in tinea pedis and tinea manuum

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Abstract

Background It has been reported that azole derivatives are useful in the treatment of dermatophytooses, also in tinea pedis and tinea manuum.

Aim The aim of the present multicentre, randomized, double-blind study was to compare the efficacy and safety of oral itraconazole with fluconazole in the treatment of tinea pedis and tinea manuum.

Patients and methods In this multicenter, double-blind, comparative study, 37 patients with tinea pedis or tinea manus were randomized to receive treatment with itraconazole (100 mg/day) or fluconazole (50 mg/day) for 30 days.

Results Two patients were not evaluable for efficacy. Both treatments reduced the number of patients with positive mycological findings, so that at the end of treatment, 64.7% of patients receiving itraconazole and 61.1% of those treated with fluconazole had negative results. Both drugs also resulted in a marked improvement in, or elimination of, all clinical symptoms; however the improvement appeared to occur more rapidly with itraconazole. The overall assessment at the end of the 6 week follow-up showed that 88.2% of patients treated with itraconazole and 72.2% of those treated with fluconazole were cured with negative mycological tests. Adverse events were reported by one patient treated with itraconazole and 5 subjects receiving fluconazole. The only changes in laboratory parameters were elevated SGOT and SGPT values in one patient in the fluconazole group, who dropped out from the study.

Discussion The results suggest that itraconazole is at least as effective as fluconazole in the treatment of tinea pedis and tinea manus, the onset of improvement in clinical symptoms is more rapid an prolonged after cessation of therapy with itraconazole, and that itraconazole appears to be better tolerated.

Keywords: Itraconazole; Fluconazole; Dermatophytosis

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Elsevier Science B.V.
SSDI 0926-9959(95)00027-5
1. Introduction

Tinea pedis is a common clinical form of dermatophyte infection. As topical treatment is often difficult, it sometimes requires systemic therapy; so does tinea manuum. Itraconazole and fluconazole are orally active triazole antifungal agents with broad spectrum activity and favourable pharmacokinetic profile [1,2]. Particularly, itraconazole has a high affinity for tissues, resulting in skin levels that are several times higher than the corresponding peak plasma levels [3]. Moreover, the drug persists considerably longer in the skin than in plasma and so its antifungal activity continues for several weeks after treatment is stopped. Results from clinical studies in patients with tinea corporis, tinea cruris, tinea pedis and tinea manuum have revealed clinical and mycological response rates of 80% or more using 100 mg/day of itraconazole [1,4,5]. In addition, itraconazole has proved superior to griseofulvin in terms of mycological clearance and clinical response in patients with dermatophyte infections. The drug also has a favourable tolerability profile, and although gastrointestinal-related symptoms are the most frequently reported it remains doubtful whether their incidence is above that observed at baseline [4].

The aim of the present multicentre, randomized, double-blind study was to compare the efficacy and safety of oral itraconazole with fluconazole in the treatment of tinea pedis and manum.

2. Patients and methods

Thirty-seven adult male and female patients, aged 18–70 years, affected by tinea pedis or tinea manuum were enrolled in this double-blind, randomized, parallel-group, comparative study conducted in two Centres in Italy (Departments of Dermatology Universities of Florence and Perugia). All patients gave their informed consent and the study was conducted in accordance with the principles of the Declaration of Helsinki, as revised in Tokyo in 1985. Exclusion criteria were considered: presence of oral or vaginal candidosis, chronic mucocutaneous candidosis, systemic mycoses, pityriasis versicolor and/or tinea corporis; previous systemic antifungal treatments within 1 month of the start of the study; unreliability; concurrent treatment with rifampicin, cyclosporin or dicoumarol anticoagulants; existence of concomitant conditions which might prevent completion of treatment.

Itraconazole (100 mg) or fluconazole (50 mg, posology usually administered in dermatophyte infections) was administered orally, in a capsule formulation, once-daily with a meal for 30 days. Concomitant treatment with any other topical or systemic antifungal drugs or topical steroids was not permitted during the trial.

Mycological testing, assessment of the clinical and subjective symptoms of infection (erythema, desquamation, vesicles, exudation, maceration, fissuring) and a physician's overall assessment were conducted at baseline, after 2 weeks of treatment, at the end of the treatment period, and 2, 4 and 6 weeks later. Clinical symptoms were scored using a 3-point scale (0 = none; 1 = moderate; 2 = severe). Mycological testing (consisting of microscope examination and culture test performed by routine techniques) was conducted on material taken from each lesion.

Any adverse events were recorded throughout the study and laboratory investigations were performed at baseline and at the end of the treatment period. Statistical comparisons were made using the Chi-square test, the Fisher's Exact test (1 and 2-tailed) and the Mann-Whitney U-Wilcoxon Rank Sum W test.

3. Results

Two of the 37 patients enrolled in the study were not included in the efficacy analysis: one, treated with itraconazole, was lost to follow-up and the other, treated with fluconazole, withdrew from the study due to elevated SGOT and SGPT levels. Of the 35 evaluable patients, 17 were treated with itraconazole and 18 with fluconazole. The demographic and baseline characteristics did not differ significantly between the two treatment groups (Table 1). Trichophyton rubrum was the most commonly isolated dermatophyte at
the basal culture test, affecting 14 patients in the itraconazole group and 13 in the fluconazole group. In the remaining 8 patients the infection was caused by *Trichophyton mentagrophytes*.

The effects of the two drugs on mycological testing conducted during the study are shown in diagrammatic form in Fig. 1. At the end of treatment, 11/17 patients (64.7%) treated with itraconazole and 11/18 (61.1%) treated with fluconazole had a negative microscopy examination. At the end of the 6-week follow-up, culture and microscopic tests were negative in 16/17 (94.1%) subjects treated with itraconazole and in 16/18 (88.9%) patients of the fluconazole group. Both *T. rubrum* and *T. mentagrophytes* appeared to respond equally well in both treatment groups. Although the differences between the treatment group at each assessment did not achieve statistical significance, the superior clinical and mycological effect of itraconazole 2 weeks after the end of treatment was of borderline significance (*P* = 0.0565).

The changes in clinical features through the study are shown in diagrammatic form in Fig. 2. Both itraconazole and fluconazole resulted in an improvement in all clinical features, with no statistically significant differences between the groups. However, the improvement appeared to occur more rapidly with itraconazole. Particularly interesting was the assessment of erythema. At baseline 13/17 patients in the itraconazole group (76.5%) and 17/18 in the fluconazole group (94.4%) had moderate erythema. However, all patients in the itraconazole group were negative for erythema 4 weeks after the end of treatment, whilst 4 of the 16 assessable patients (25%) in the fluconazole group still showed moderate symp-

### Table 1
Demographic and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Itraconazole (n = 17)</th>
<th>Fluconazole (n = 18)</th>
</tr>
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<tbody>
<tr>
<td>Male/female</td>
<td>15/2</td>
<td>13/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.9 ± 14.4 (19–63)</td>
<td>38.8 ± 11.2 (18–58)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Tinea pedis + t. manuum</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Duration of mycosis (months)</td>
<td>10.4 ± 13.9 (0.7–60)</td>
<td>15.0 ± 29.6 (0.5–120)</td>
</tr>
</tbody>
</table>

Values given as mean ± SD (range).

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Fig. 1. Results of the mycological assessments in patients with tinea pedis/tinea manuum treated with itraconazole (100 mg/day) or fluconazole (50 mg/day) for 30 days.
tom. This difference between the treatment groups was statistically significant ($P = 0.0279$).

An overall assessment conducted at the end of study showed that 15 patients (88.2%) treated with itraconazole were considered cured with negative mycological tests, whilst two (11.8%) had minor residual lesions. In contrast, 5 patients (27.8%) treated with fluconazole still had minor residual lesions, with 13 (72.2%) being rated as cured with negative mycological tests (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Overall assessment</th>
<th>Itraconazole ($n = 17$)</th>
<th>Fluconazole ($n = 18$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured with negative mycology test</td>
<td>15 (88.2%)</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>Residual lesion with negative mycology test</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Residual lesion with positive mycology test</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

All 37 patients were evaluated for tolerability. Adverse events were reported by one patient treated with itraconazole and 5 patients treated with fluconazole. Itraconazole was associated with stomach pain, whilst patients treated with fluconazole reported loss of libido and drowsiness (one patient), feeling sick (one patient), stomach pain (one patient), headache (one patient), and elevated SGOT and SGPT levels (one patient). This latter patient was withdrawn from the study. There were no other clinically relevant changes in laboratory parameters in either group.

4. Discussion

Both itraconazole and fluconazole reduced the number of patients with positive mycological findings, so that by the end of treatment, 64.7% in the itraconazole group and 61.1% in the fluconazole group were negative. However, itra-
conazole was associated with a more marked increase than fluconazole in the percentage of patients with negative results over the 6-weeks follow-up period. *T. rubrum* and *T. mentagrophytes* responded equally well to both treatments. Both treatments also produced improvements in the clinical features of the condition, although the improvement tended to occur more rapidly with itraconazole, with a more quick assessment of erythema. An overall assessment, conducted at the end of the study, showed that 88.2% of patients treated with itraconazole and 72.2% treated with fluconazole were cured with negative mycological tests. The remaining patients had minor residual lesions. The more sustained action of itraconazole may be due to preferential uptake by keratinous tissues leading to persistence of therapeutic levels in skin tissues.

Itraconazole was very well tolerated, with only one patient reporting an adverse event (stomach pain). In contrast, adverse events were reported by 5 patients treated with fluconazole. The only clinically relevant changes in laboratory parameters were elevated SGOT and SGPT values in one patient in the fluconazole group who was the only patient withdrawn from the study due to adverse events.

Previous double-blind, comparative studies conducted in patients with tinea pedis and/or tinea manus have shown oral itraconazole (100 mg/day) to be significantly superior to oral griseofulvin (500 mg/day) with respect to the mycological cure rate and similarly effective with respect to the clinical cure rate [5].

The result from this study suggest that itraconazole is at least as effective as fluconazole in the treatment of tinea pedis and tinea manus with a more rapid and sustained action. Moreover, itraconazole appears to be better tolerated, without any adverse effects on liver function tests.

References


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