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# Itraconazole in Onychomycosis

## *Open and Double-blind Studies*

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**Fifteen patients with onychomycosis caused by *Trichophyton rubrum* or *T. mentagrophytes* were treated with 50 mg itraconazole daily for 3 to 6 months. Fingernail infections were cured in two patients and two responded with marked improvement, e.g. small residual lesion remained and positive microscopy. The infected toenails were markedly improved in nine of 13 patients. Twenty-seven patients with *T. rubrum* infected nails were given 100 mg itraconazole daily for 6 to 8 months. Fingernails were cured in nine of eleven patients, while toenail infections were cured in one and markedly improved in 14 of 25 cases. Responses to 100 mg itraconazole versus 500 mg griseofulvin daily for 6 months were compared and evaluated in 20 patients with onychomycosis caused by *T. rubrum* or *T. mentagrophytes*. Fingernail infections responded equally well to both drugs with half of the cases cured or markedly improved, whereas toenails responded better to itraconazole, e.g. 4 of 9 were markedly improved versus one of 10 on griseofulvin. In patients given 50 mg itraconazole daily a significantly better response was observed in persons below 30 years of age compared to older individuals. Also, side-effects which were mainly mild and located to the gastro-intestinal tract or the central nervous system were seen less often in this group of patients on the low dose. Follow-up studies showed that cured nails remained cured, that markedly improved toenails continued to improve until cure in three of 21 patients but that aggravation took place through the one year of follow-up in more than half of the patients evaluated as markedly improved at the end of treatment.**

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Like its predecessors miconazole and ketoconazole, the novel triazole itraconazole has an antifungal activity in vitro against most of the fungi of medical and veterinary interest including dermatophytes, Candida, Cryptococcus, Pityrosporum, Aspergillus, etc. Animal experiments have confirmed that itraconazole has a broad-spectrum activity of low doses in various superficial mycoses and revealed no side-effects (1). In man, clinical studies have been carried out in more than 3000 patients with superficial and systemic mycoses. As far, it appears that itraconazole may be a valuable antifungal for short oral treatment of uncomplicated superficial fungal infections, and may be of benefit too in some systemic opportunistic infections (2). The value of the drug in onychomycosis was studied in two open studies in which results obtained with daily doses of itraconazole of 50 or 100 mg were compared and in a double-blind study, where itraconazole 100 mg daily was compared to griseofulvin 500 mg.

## MATERIALS AND METHODS

### *Patients*

1. In the first study 15 patients were included, two females, aged 21 and 54, and 13 males, 11–68 years (mean 41 years). Two patients had fingernail infection only, 11 toenails only, and two had both finger- and toenail mycosis. Six of 13 patients with infected toenails were less than 30 years old, seven between 31 and 60 years old. *Trichophyton rubrum* was isolated from all 15 patients and, in addition, *T. mentagrophytes* was found in one. The duration of onychomycosis was from two to 40 years (average 11.3 years).

2. The second study comprised 27 patients, nine females aged 13–52 years (mean 37 years), and 18 males aged 21–75 years (mean 47 years). Fingernail mycosis was present in two, toenail mycosis in 16, and combined toe–fingernail infection in 9 patients. *T. rubrum* was isolated from all the patients. The duration of mycosis was 2–50 years (average 11.8 years). Twenty-four patients had previously been treated with griseofulvin for up to two years, and nine with ketoconazole for up to eight months. One patient was untreated.

3. In the double-blind study nine females, aged 40–69 years (mean 55 years) and 11 males aged 13–76 years (mean 48 years) were included. One female had the fingernails affected, 14 patients toenails, and combined finger–toenail infection was present in five. The dermatophytes involved were *T. rubrum* in 18 and *T. mentagrophytes* in two. In addition, *Candida albicans* was present in the fingernails of three patients. The onychomycosis had lasted for two to 30 years (average 12.5 years).

Most of the patients in all three groups had previously received treatment with griseofulvin or ketoconazole but without success due to side-effects, short duration of therapy or ineffectiveness. None of the patients had received antimy-

cotics within one month before the start of the study and none were pregnant or suffered from serious concurrent diseases.

*Methods*

Before treatment, every second month during, and at the end of treatment the patients were evaluated clinically, mycologically and with laboratory tests. The clinical examination included evaluation of brittleness, onycholysis, subungual keratosis and perionyxis. At each visit and at the end of treatment the involved zone of each nail was shaded on a figure in the record and the percentage of involved nail was estimated. The mycological examination included KOH preparation and microscopy as well as Sabouraud-cycloheximide-chloramphenicol agar cultures. Laboratory tests included haemoglobin, leucocyte count, platelet estimate, creatinine, alcaline phosphatase and alanin-amino-transferase (ALAT).

*Treatment*

In the first study the patients were given 50 mg itraconazole once daily for 3–6 months, taken with a meal. In the second study the daily dose was 100 mg for 6–8 months. In the double-blind study patients received griseofulvin or itraconazole on a randomized basis. For each patient, 12 boxes were prepared, each containing blister packs with $3 \times 10$ capsules. Each capsule contained either 250 mg griseofulvin or 50 mg itraconazole. The daily dose was 2 capsules taken just before breakfast for 6 months.

Response to treatment was evaluated clinically and mycologically. Cure was complete absence of clinical lesions and negative mycology. Marked improvement was the score given to nails almost clinically cured, with positive microscopy and negative culture. Improvement was the response in patients who had obtained a tolerable condition with at least 50% improvement compared to baseline condition.

## RESULTS

*Study I*

The response to 50 mg itraconazole is given in Table I. The duration of treatment until improvement was 2–6 weeks in fingernail- and 6–8 weeks in toenail infections. In five patients with a poor response after 4 months the daily dose was increased to 100 mg for 4 months leading to a better clinical response. However, no toenails were completely cured. Infections of the toenails in six patients under 30 years of age responded significantly better than toenail infection in seven above that age ($p=0.005$). Side-effects were minor and observed in one patient who complained of diarrhoea and loss of appetite. Laboratory values were within normal limits throughout the study. After the end of treatment, nine patients were seen in follow-up examinations after 6 and 12 months. Cured fingernails stayed cured. Markedly improved toenails stayed unchanged in four but deteriorated in five, even (not) to baseline condition.

*Study II*

Results are given in Table I. Durations of therapy needed for cure of the fingernail infection and for marked improvement of the toenail infection were, on average, 4 months and 7 months, respectively. Three of the patients evaluated as improved wanted to stop treatment after 4 months due to side-effects. One was unevaluable as treatment lasted for one week only due to invalidating headache, gastritis and diarrhoea.

A total of 9 patients complained of mild side-effects comprising headache, dizziness, tiredness, depression, nausea and various gastro-intestinal symptoms. Raised liver enzymes (ALAT) were observed in one patient after 6 months of treatment. The level increased to 200 ($n<40$) and decreased to normal 3 months after cessation of the drug. Thus, the number of patients with adverse reactions was significantly higher in those who received 100 mg itraconazole daily ($p=0.003$) than in those on a 50 mg daily dose. Sixteen patients were examined 6 and 12 months after end of treatment. In four markedly improved patients, improvement continued for several months, five remained stationary and in seven deterioration was seen after 12 months. Cured nails did not relapse.

*Study III*

The distribution of patients given griseofulvin or itraconazole and the responses to treatment are given in Table II. One patient on griseofulvin left the study after one month due to severe gastritis and three after three and four months, respectively, due to lack of efficacy. That was also the reason for cessation of treatment in two patients on itraconazole after four months. One of these additionally complained of gastritis. Another patient on itraconazole suffered from extreme tiredness, but apart from that no side-effects were observed. Laboratory tests were within normal ranges throughout the study in both groups.

The clinical and mycological responses to itraconazole versus griseofulvin did not differ considering the fingernail lesions, but there was a tendency to a better response to itraconazole in the toenail lesions (RR = 6.4).

In the griseofulvin group, six patients who had responded with improvement, no change, or side-effects were offered itraconazole for up to six months. Four of these responded with marked improvement, one with cure, and one improved from unchanged. Two patients were lost to follow-up and in the remaining two the lesions were stationary throughout

Table I. *Results of treatment of dermatophytosis ungvium with itraconazole 50 and 100 mg oral dose, respectively*

Cure = complete absence of clinical lesions and negative mycology. Marked improvement = minimal residual lesions, positive microscopy and negative culture. Improvement = at least 50% improvement compared to baseline and positive mycology

| | Daily oral dose of itraconazole | | | |
|---|---|---|---|---|
| | 50 mg, $n=15$ | | 100 mg, $n=27$ | |
| Clinical and mycological response | Fingernails $n=4$ | Toenails $n=13$ | Fingernails $n=11$ | Toenails $n=25$ |
| Cure | 2 | – | 9 | 1 |
| Marked improvement | 2 | 9 | 1 | 14 |
| Improvement | – | – | 1 | 9 |
| No change | – | 4 | – | – |
| Unevaluable | – | – | – | 1 |

the one year of follow-up. In the itraconazole group, deterioration through 12 months of follow-up were seen in three patients who had responded with marked improvement. Four patients who deteriorated or responded with improvement or no change were given additional treatment with double dose for up to six months. This improved the responses markedly, but complete cure was not obtained. One patient with toenail lesions evaluated as markedly improved at the end of treatment was cured at the six months follow-up without further treatment. Finally, one patient in this group in whom *Candida albicans* was persistently isolated from one fingernail was cured with one month of ketoconazole 200 mg daily dose.

*Study I, II, III*

A total of 29 patients, who had all received at least 100 mg itraconazole daily for at least 6 months, were seen one year after end of treatment. The observations included that nails cured at the end of treatment did not relapse, that markedly improved toenails in three females continued to improve until cure, and that markedly improved toenail infections aggravated through the one year of follow-up in 13 of 21 patients.

## DISCUSSION

The clinical and mycological responses to a daily dose of 50 or 100 mg itraconazole in onychomycosis indi-

Table II. *Results of double-blind study on dermatophytosis ungvium treated with either itraconazole or griseofulvin*

For explanations of the clinical responses see Table I

| | Daily oral dose | | | |
|---|---|---|---|---|
| | 100 mg itraconazole, $n=10$ | | 500 mg griseofulvin, $n=10$ | |
| Clinical and mycological response | Fingernails $n=4$ | Toenails $n=9$ | Fingernails $n=2$ | Toenails $n=10$ |
| Cure | 1 | – | 1 | – |
| Marked improvement | 1 | 4 | – | 1 |
| Improvement | 1 | 3 | – | 5 |
| No change | 1 | 2 | 1 | 3 |
| Unevaluable | – | – | – | 1 |

cate that this treatment is of benefit in fingernail infections, in which cure or marked improvement is obtained after average four months in 16 of 19 patients (84.2%). In toenail infections a daily dose of 50 or 100 mg for 6 to 8 months resulted in cure or marked improvement in 28 of 47 patients (59.6%). Recently, Hay et al. reported response rates of 90% in fingernail and 76% in toenail infections. These more favourable results may be explained by longer duration of treatment, i.e. average 5.4 and 10.3 months, respectively (3). A good response was significantly related to young age but not to duration of disease. It is noteworthy that the 50 mg dose gave relatively good results, especially in young patients, and that side effects were less frequent. Further studies using a dose of 50 mg in young patients and a duration of therapy for more than eight months might therefore be indicated. In the double-blind study the responses to itraconazole tended to be better than those to griseofulvin. Due to the small groups, significance was not present. However, final results of the multicenter study in which the present study will be included may confirm this finding. On the other hand, it might be speculated whether the usually recommended daily dose of 500 mg griseofulvin is on the whole, sufficient for toenail infections. However, the results indicate that itraconazole is of obvious value in patients unsuccessfully treated with griseofulvin.

The value of the treatment was estimated at follow-up visits after 6 and 12 months. The findings showed that cured nails stayed cured, but that even small residual lesions at the end of treatment were able to cause relapses. Aggravation of onychomycosis in the follow-up period was not related to either age, dose of itraconazole or duration of disease. In a small number, improvement continued after end of treatment until spontaneous cure. Thus, to obtain satisfactory results of the treatment of onychomycosis it seems important to treat until clinical and mycological cure. In the toenail infections, none of the presently available antimycotics used solely are capable enough, even after prolonged duration of treatment, which again increases the risk for side-effects or development of tolerance to the drug. However, recent studies in which a traumatic removement of diseased nail tissue is combined with specific topical or systemic antimycotic treatment have been very successful (4, 5, 6). It might also be speculated if pulse therapy would be of benefit for onychomycosis, for example, as one or probably more capsules given with weekly or monthly intervals.

Adverse reactions were mild, related to the gastrointestinal tract or the central nervous system and more frequent in patients receiving 100 versus 50 mg itraconazole daily. The finding in one patient of transient raised ALAT stresses the importance of repeated control of blood parameters during prolonged treatment, e.g. in onychomycosis. Itraconazole like ketoconazole may be hepatoxic although clinical studies so far have shown it to be widely harmless.

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