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Tioconazole nail solution—an open study of its efficacy in onychomycosis

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Summary

In view of the problems encountered in the treatment of onychomycosis with orally administered antifungal drugs, alternative forms of therapy are needed. Tioconazole (28%) nail solution is a new topical preparation for use on infected nails. In this study 27 patients received treatment with tioconazole (28%) for up to 12 months. Six patients (22%) achieved complete clinical remission and were free of infection at follow-up, 3 months after therapy. They included infections caused by *Trichophyton rubrum* (4), *Hendersonula toruloidea* (1) and *Acremonium* (1). Apart from the latter, all infections responding to treatment were in the finger nails, even though three patients had active infection in the toe nails as well which did not respond to therapy. Significant improvements were recorded in a further 11 patients. They did not, however, achieve complete clinical and mycological recovery. The results indicate that cures of onychomycosis are possible after topical therapy, and further methods of using this form of treatment such as combined surgical and topical therapy are discussed.

Tioconazole is an imidazole antifungal agent of established value in the topical treatment of superficial mycoses (Kuokkanen, 1981; Clayton *et al.*, 1982; Grigoriu & Grigoriu, 1983). It has a broad spectrum of anti-fungal activity with a minimum inhibitory concentration (MIC) range of 0·2–25·0 $\mu g\ ml^{-1}$ for common dermatophytes and 0·2–12·5 $\mu g\ ml^{-1}$ for *Candida albicans* (Jevons *et al.*, 1979). MIC values against mould fungi which less commonly cause onychomycosis (e.g. *Scopulariopsis brevicaulis* and *Hendersonula toruloidea*) usually exceed 25 $\mu g\ ml^{-1}$. Tioconazole has been shown to be effective in dermatophytosis and superficial *Candida* infections including vaginal candidosis as well as pityriasis versicolor (Rieth, 1983). Normally, the drug is prescribed in 1% or 2% cream formulations, although an ointment containing 6% tioconazole is under investigation for single dose treatment of vaginal candidosis (Artner, 1983).

Treatment of nail infections caused by fungi is both difficult and lengthy. It has been estimated that less than 40% of onychomycoses of the toe nails caused by dermatophytes can be cured by griseofulvin (Davies, 1967) or ketoconazole (Hay & Clayton, 1982). The results are better in finger nail infections. Onchomycosis caused by mould fungi other than dermatophytes does not usually respond to chemotherapy. The only therapeutic alternatives at present are surgical avulsion or chemical removal using 40% topical urea (White & Clayton, 1982), but in both cases the relapse rate is high.

We have evaluated a new formulation of tioconazole nail solution—tioconazole (28%) as the sole treatment for onychomycosis in an open study. The compound is presented as a solution which can be applied to infected nails as a daily treatment.

Patients and methods

All patients entering the study had onychomycosis confirmed by culture and/or direct microscopy. None had received specific antifungal treatment for a period of 2 months preceding the study. Informed consent was obtained from all patients who were also instructed not to apply varnish or other nail preparations to nails under treatment.

The following laboratory tests were carried out before treatment and at monthly intervals thereafter: full blood picture, liver function tests, urea, creatinine, glucose. The urine was tested for blood, sugar and protein at each visit.

All patients were instructed to paint the solution onto infected nails twice daily. The initial period of therapy was 3 months, but this was extended up to a maximum of 12 months at the discretion of the investigators. In view of the length of the proposed study only the active compound was assessed. A clinical assessment of the extent of infection and clinical improvement, as well as direct microscopy and cultural examination were carried out monthly for the first 3 months and every 2 months thereafter. The percentage of the surface area of involved nails was estimated at each visit. Note was made of infection in adjacent sites and, if present, this was treated by application of 1% tioconazole cream twice daily until the site was clinically and mycologically free of infection. At the end of therapy patients with completely normal nails and negative direct microscopy were rated as cured. Improvements were scored as '++' or '+' depending on whether less than 50% or more than 50% of the affected nail remained clinically and microscopically infected. Patients were seen at follow-up 6 weeks and 3 months after conclusion of therapy.

The studies were carried out at St. John's Hospital for Diseases of the Skin, London, and the Western Infirmary, Glasgow.

Results

A total of 27 patients (15 males and 12 females) completed at least 3 months of treatment. The duration of treatment ranged from 2 to 12 months, and 14 patients received more than 3 months of therapy. Ten patients had infections confined to the finger nails, 13 the toe nails, and in four both sites were involved. Eighteen patients had received previous systemic treatment with either griseofulvin or ketoconazole which had been unsuccessful.

Table 1. Tioconazole (28%)—results of treatment

	Numbers of patients	Clinical improvement		No clinical improvement	Clinical and mycological remission
		++	+	0	
Dermatophyte Infections	18	8	4	2	4*
Candidosis	1	0	0	1	0
Hendersonula toruloidea	3	0	1	1	1*
Acremonium sp	1	—	—	0	1
Unclassified (culture negative)	4	3	0	1	—

* Finger nail infections

The organisms isolated before treatment are shown in Table 1. Most patients showed a pattern distal and lateral subungual onychomycosis, DLSO (Zaias, 1972). One patient had superficial white onychomycosis (SWO) of the toe nails caused by *Acremonium* sp.

The results of treatment are shown in Table 2. Six patients were found to be clinically and mycologically free from infection after 2–7 months (mean 5·2) of treatment (Figs. 1a, 1b). They included the one patient with SWO caused by *Acremonium* spp. as well as four patients with infections caused by *T. rubrum* and one individual with onychomycosis caused by *H. toruloidea*. Eleven patients showed marked improvement (++) on subjective assessment whereas there was little (+) or no improvement in five and five individuals respectively. Of those patients who were cured, all remained free of infection at 6 weeks and 3 months after completion of treatment. The patient with SWO relapsed 6 months after the end of therapy. A total of 145 nails were assessed. At the beginning of treatment the mean area of nail involvement in these patients was 66% (±35). The mean improvement recorded at the end of treatment in the area of nail involved was 29% (±30) for all treated nails; but in 114 nails showing any clinical improvement the mean area of new nail growth was 37% (±31).

Table 2. Fungi isolated before therapy

Fungus isolated	Finger nails	Toe nails	Both sites
Candida albicans	1	0	0
Dermatophyte*	5	10	3
Acremonium species	0	1	0
Hendersonula toruloidea	2	0	1†
Unclassified (culture negative)	2	2	

* Includes *Trichophyton rubrum* (17), *T. soudanense* (1).
† Includes *H. toruloidea* in toe nails, unclassified finger nails.

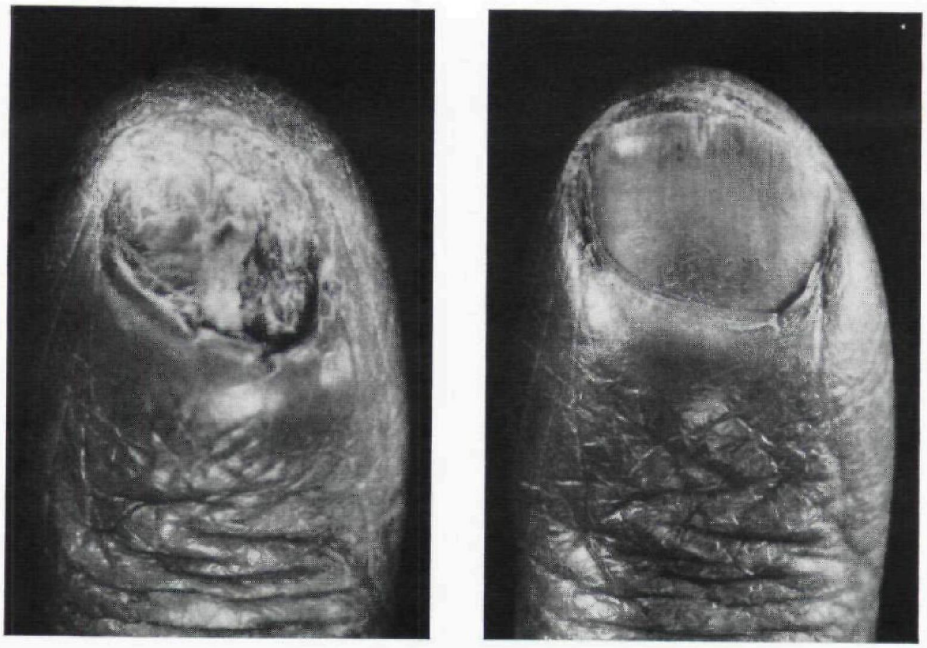

Figure 1. *T. rubrum* infection of the fingernail (a) before treatment, (b) after 7 months of tioconazole (28%) nail solution.

The blood tests were compared with pre-treatment values using Wilcoxon's signed rank test and Student's *t*-test. No significant change in laboratory values was recorded.

Discussion

This study has shown that six (22%) of 27 patients receiving tioconazole (28%) nail solution for onychomycosis caused by *Acremonium* spp. Three of the responding group had infections of the of infection 6 months after the end of treatment. The infections responding to treatment were onychomycosis of the finger nails in all cases apart from the one patient with superficial white onychomycosis caused by *Acremonium* spp. Three of the responding group had infections of the toe nails as well which did not clear completely on treatment. A further 11 patients showed marked improvement as judged by the investigators whereas 10 showed minimal improvement or failed to respond. It was found that mycological assessment by cultural isolation was not possible during treatment because no growth was obtained from any nail, presumably reflecting the inhibitory effect of tioconazole remaining in the nail matrix. The treatment appeared to be safe and patients found the solution easy to apply. Some glazing of nail plates occurred but this disappeared after cessation of treatment.

Spontaneous remission of dermatophyte or *Hendersonula* infections of the nail plates are exceptionally rare, and therefore some form of therapeutic intervention offers the only real chance of recovery. Most of the patients receiving treatment in this study had already failed to respond to systemic therapy. This included three of those who achieved complete remission on tioconazole alone. There are therefore a number of conclusions which can be drawn from this

investigation. In some patients it is possible to obtain clinical and mycological cures in onychomycosis using topical therapy alone. This is of potential value to patients because the use of prolonged administration of systemically active drugs is thus avoided. Five of the six responders had full thickness involvement of the nail plate, including the superior aspect, and it is possible that abrasion of this surface using a dental burr or an emery board might enhance the penetration of drug into the nail. These five patients all had finger nail involvement. In view of the encouraging response recorded here it may be possible to obtain better results by using tioconazole (28%) solution either in combination with griseofulvin or ketoconazole, or (following removal of the nail plate) with urea. Further studies along these lines are in progress.

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