

A DOUBLE-BLIND CONTROLLED TRIAL OF WHITFIELD'S OINTMENT AND VARIOTIN IN RINGWORM INFECTIONS WITH A TWO YEAR "FOLLOW-UP"

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Abstract. A double-blind controlled trial comparing the therapeutic efficacy of Whitfield's ointment and Variotin was carried out on 14 patients with tinea infections. Twelve had tinea pedis and two had tinea corporis. All infections were due to either *T. rubrum* or *T. interdigitale*. Initial treatment period was 8 weeks and those patients not cured were subsequently treated for a similar period with the alternative fungicide. Follow-up studies continued for 2 years. Variotin was found to be as effective as Whitfield's ointment. One-half of the patients seemingly cured by either Variotin or Whitfield's ointment relapsed during the following 12 months and their toeweb seemed to have become reinfected from clinically not obvious onychomycosis. The trial confirmed the therapeutic efficacy of Variotin against ringworm infections, including *T. rubrum*, of glabrous skin. There were no side effects.

A preliminary multicentre trial (2) had indicated that pecilocin (Variotin, Leo Laboratories) was an effective topical application against common dermatophytes, including *T. rubrum* on glabrous skin. It was felt that a double-blind trial comparing the therapeutic efficacy of Variotin with Whitfield's ointment (Benzoic Acid Compound ointment, B.P.C.), an established topical fungicide, containing 6% benzoic acid and 3% salicylic acid, should be undertaken and be combined with a prolonged follow-up study. The trial was arranged at only one centre to ensure uniformity of treatment, follow-up of patients and laboratory techniques.

INVESTIGATION

Patients

As it seemed important that patients taking part in such a trial could be relied upon to carry out their instructions and were available for prolonged follow-up studies, most of the 14 patients selected were doctors, dentists, their

wives and medical students. Twelve patients had tinea pedis, in 8 due to *T. rubrum*, and in 4 due to *T. interdigitale*, affecting toeclfts and plantar skin but without clinically obvious nail involvement. Two had tinea corporis, both due to *T. interdigitale*.

Trial arrangement

Whitfield's ointment and Variotin ointment were supplied, coded, by Leo Laboratories in identical tubes and were issued by the hospital pharmacy to patients in a "randomised double-blind trial" arrangement drawn up by Professor D. J. Newell, Department of Medical Statistics, University of Newcastle upon Tyne.

The initial treatment period was 8 weeks. Patients were instructed to apply their ointment every night after washing their feet with warm water to which a small quantity of a liquid detergent had been added and after drying the skin with tissue paper. Ointments were massaged into the toeclfts for 2-3 min. Patients were first assessed 3 months after treatment had been started, i.e., 1 month after it had been stopped. Scrapings were taken for fungal culture either from still affected or previously affected skin. If there was either clinical or/and mycological evidence of persisting skin infection, patients were then given by the hospital pharmacy the other fungicidal ointment and were asked to use the same technique for a second period of 2 months. Three months after such a "cross-over" of ointments patients were again examined clinically and fungal cultures were set up from previously or still affected skin. All patients were similarly examined at 3-monthly intervals for the subsequent 18 months, i.e., for a total of 2 years.

Mycology:

Scrapings were taken using a tenotome and nailshavings were obtained from dystrophic areas and during later stages of the trial also from not obviously infected nailplates near the nailfolds. Scrapings were cultured independently in the mycology laboratories of the Hospital Department of Microbiology and of the Department of Dermatology within 24 hours on dextrose-peptone agar containing chloramphenicol 50 mg/l and cycloheximide 500 mg/l and incubated for at least 1 week at 29°C.

RESULTS

After 3 months. The 2 patients with tinea corporis due to *T. interdigitale* were found to be clinically and mycologically free from fungal infection and they did not relapse. Both had been treated with Variotin.

Of the remaining 12 patients with tinea pedis 5 had been treated with Variotin (1 for *T. interdigitale* and 4 for *T. rubrum* infection) and 7 with Whitfield's ointment (3 for *T. interdigitale* and 4 for *T. rubrum* infection). Only 2 patients, both with *T. rubrum* infection, required a "cross-over" to the alternative treatment; 1 had been treated with Whitfield's ointment and the other with Variotin.

After 6 months. The patient who had been treated with Variotin and then with Whitfield's ointment still had interdigital scaling from which *T. rubrum* could again be cultured. The other patient's toeweb looked clinically normal but again yielded *T. rubrum* on culture. Three other patients who appeared clinically and mycologically clear 3 months after the start of the trial were again found to have *T. rubrum* in their toeweb. Two of these had been treated with Whitfield's ointment and the third with Variotin. The remaining 7 patients seemed cured and had negative cultures.

While at the beginning of the trial patients with obvious clinical and mycologically proven tinea of toenails were excluded from this study, scrapings were unfortunately cultured only from clinically infected nails. At the 6-months stage, however, fine shavings from all toenails of the five still affected patients were cultured and *T. rubrum* was found in one or more toenails of all 5 patients. The 4th and 5th nails usually harboured the fungus although they showed only slight dystrophy and did not look obviously mycotic. These 5 patients were asked to apply Variotin in future each night to all toenails and nailfolds as well as to their toe-clefts.

After 9 months. Only 1 of these 5 patients still had *T. rubrum* in his toe-clefts, all 5 still had positive nailcultures. None of the other patients had relapsed clinically but nailscrapings from the 5th toe yielded *T. rubrum* on culture in 2 further patients. Both these patients were given Variotin to apply to all toenails and nailfolds and their toeweb remained free from tinea for the subsequent 15 months.

After 12 months. No change.

After 15 months. Nailcultures remained positive in all 7 patients, but their toe-clefts were clinically and mycologically free from tinea infection and their nails looked even less dystrophic.

After 18 months. No further skin lesions were seen in any patient and fungal cultures were negative although toe-clefts had not been treated for at least 6 months. Although the nails looked virtually normal one or more toenails still yielded *T. rubrum* on culture in these 7 patients. None of the patients showed evidence of irritation or sensitization to either fungicide.

T. RUBRUM INFECTION OF TOE-NAILS TREATED WITH VARIOTIN

Three other patients with longstanding gross *T. rubrum* infection of all toenails have been treated for almost 3 years with Variotin ointment. While the initial results were encouraging and in all patients up to two-thirds of the nailplates looked clinically normal, cultures for *T. rubrum* remained positive, at least intermittently, from the proximal dystrophic nail, the nail bed and the nail matrix.

All patients had previously been treated at other centres with oral Griseofulvin for long periods and two had had their toenails avulsed before Griseofulvin had been given. These 3 patients are now being treated with oral Griseofulvin as well as with Variotin.

DISCUSSION

This double-blind, "cross-over" trial comparing the fungicidal effect of Variotin with Whitfield's ointment, the most established of topical fungicides in England, has confirmed that Variotin is of at least comparable therapeutic efficacy.

The beneficial effect of Whitfield's ointment may be due to its ability to kill spores and to remove infected debris but many patients find its irritant effect unacceptable even on their feet and discontinue treatment.

The rather disappointing relapse rate of patients apparently cured by either Whitfield's ointment or Variotin appeared to be associated with, clinically not always obvious, *T. rubrum* infection on the 4th and 5th toenails, areas not adequately accessible to surface applications. However, long-

term treatment with Variotin combined with oral Griseofulvin may be successful in so far incurable *T. rubrum* infections of nails as Variotin seems to be able to attack superficial ringworm infection of nails while Griseofulvin is necessary to deal with the deeper infections of the nail, nailmatrix and nailbed. It seems possible that Griseofulvin failed to cure ringworm infections of nails even when given continuously for 1 year or more because infected debris remained in the nailfold or nailsac and acted as reservoir of reinfection. These sites may be accessible to a potent topical fungicide. The well known high relapse rate of tinea infection of toewebs seems to be due in many cases to reinfection from infected toenails which may look clinically normal.

In 1967 Wethered et al. (3) reported a double-blind trial comparing the therapeutic effect of Tinaderm (tolnaftate, Glaxo Laboratories), and later of Variotin with suitable bland applications using the equally infected paired limbs of 12 mentally retarded patients confined to an institution. Each fungicide was tested in this way for 28 days, and the interval between the Tolnaftate and Variotin trial was 2 months. A therapeutic effect could not be demonstrated by these authors for either Tolnaftate or Variotin during their trials. The ointments, control as well as the supposed fungicide, were applied by members of the nursing staff and as each patient removed his socks they were put into the appropriate shoes. However, English et al. (1) established in the same residential institution that dermatophyte fungi could be isolated from socks of infected persons both before and after laundering and it must be assumed that patients' socks were changed more often than every 28 days. These authors also suggested that cross infection was likely to occur from dormitory and bathroom floors. It was certainly even more likely to spread from one foot to another in the same individual, facilitated, no doubt, by rubbing or scratching of toeclefts while in bed. Wethered et al. also suggested themselves that the treatment period of 28 days may have been too short.

The duration of treatment of tinea pedis has always been empirical, varying widely from author to author. Unfortunately the epidermal turnover time at this site, affected or unaffected by fungal infection, has not yet been established. This information is essential to determine the

minimum period of treatment, although it is unlikely to exceed the 8-week treatment period used during this trial for the treatment of glabrous skin infections.

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REFERENCES

1. English M. P., Wethered R. R. & Duncan E. H. L.: Studies in the epidemiology of Tinea Pedis VIII: Fungal infection in a longstay hospital. *Brit Med J* 3: 136, 1967.
2. Holti, G., Lyell, A., McCallum, D. I., Morgan, J. K. & Smith, P. A. J.: Ringworm treated with Variotin ointment. *Brit J Derm* 78: 661, 1966.
3. Wethered, R. R., Heeler, W. R. & Warin, R. P.: Clinical trials of Tolnaftate and Variotin. *Brit J Derm* 79: 352, 1967.

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