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The Unexpectedly Rapid Response of Fungal Nail Infection to Short Duration Therapy

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To test our hypothesis that, by laying down a fungicidal barrier in the growing nail, a short course of antifungal therapy should be effective against onychomycosis, we treated 8 subjects with *Trichophyton rubrum* nail infection with terbinafine 125 mg b.d. for 14 days. All but one patient showed marked improvement, and 80% of fingernails and 37% of toenails were clinically cured after 6 months. Although this confirmed our prediction, the onset of response measured by outward movement of affected nail and negative cultures from distal nail clippings occurred after as little as 4 weeks. This was too soon for a fungicidal barrier to have grown out and indicates that the drug must have been carried directly into the diseased distal nail, presumably from newly formed ventral nail beneath it. The findings show that 1) short duration therapy, perhaps even a single dose, is possible in fungal nail infections; 2) the ventral nail provides unexpectedly rapid access of drugs to the site of distal disease. ***Key words: Terbinafine; Allylamines; Nail bed.***

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This study was done to test our hypothesis that in fungal disease of the nails an effective agent should work in just a few doses, and consequently that the conventional systemic therapy which is given continuously for months if not years (1,2) is unnecessarily prolonged.

The nail plate grows mainly from the root matrix, which extends from beneath the nailfold to the edge of the lunula, and it is generally believed therefore that anti-fungal drugs pass into the nail plate during its formation in the root. If this is true, then a drug which maintains antifungal activity in the nail will be carried outward as a band in nail plate and bed (3), forming a barrier to fungal invasion.

Surprisingly, it seems not to have been realised, consequently, that it is the leading edge formed by initial doses of the drug that achieves the therapeutic effect, and therefore that there is no need to persist with administration of the drug for months or years. Thus a short course of treatment, perhaps even a single bolus dose, should be adequate; giving treatment as recommended (3) until the nail appears normal is unnecessary. The original view of how a drug reaches the nail (3) has to be modified now that we know that in addition to growth from the matrix, new nail is continuously added to the ventral surface by the nail bed epithelium as the nail grows out (4,5); but this additional ventral barrier to fungal invasion (Fig. 1) appears only to strengthen our hypothesis.

To test the hypothesis we chose terbinafine (Lamisil, Sandoz), a powerful fungicidal allylamine which has been effective in onychomycosis when given at a daily dose of 250 mg for 6 to 12 months (6,7,8). Although the drug could not be made available to us for treatment with a single dose, we treated patients with the same dose for the deliberately short period of 14 days, and observed the subsequent growth of the affected nails and movement of the diseased zone for 6 months.

PATIENTS AND METHODS

Eight patients (6 males and 2 females; mean age 37 years, range 21–59) with distal onychomycosis were studied. Two had disease of toe nails only while in 6 both finger- and toenails were involved. All had been found to have infection with *T. rubrum* on mycological culture of nail clippings, which was confirmed in clippings sent to a second laboratory. None had been treated with other systemic antifungal agents in the previous 12 months. One patient had manic depressive psychosis controlled by lithium carbonate, one was taking dipyridamole following a stroke, and one was taking hormone replacement therapy with conjugated estrogens. The subjects were otherwise healthy, and standard laboratory tests of renal, hepatic and haematological function were normal. The study was approved by the hospital ethics committee, and all subjects gave written informed consent after receiving full explanation of the nature of the study.

The number of affected finger- and toenails was recorded in each patient, and the most severely affected nail that was nonetheless not too dystrophic to measure was chosen for detailed study. After treatment with terbinafine, 125 mg orally twice daily for 14 days, patients were seen at 4-weekly intervals up to 24 weeks, and then at 36 and 48 weeks. At all visits, distal clippings were taken from the designated study nail for mycological microscopy and culture.

For fungal disease of the nail to persist (and spontaneous cure is rare) inward movement of the fungus must be equal to or greater than the rate of outward movement of the nail plate. To measure the speed of onset of the drug effect, it was therefore necessary to record the movement of the affected segment and to compare this with the rate of growth of the nail. To do this we developed a novel *transfer method* based on the method we use for measuring weal area, in which an ink-marked outline of the reaction is transferred to paper, by means of adhesive cellophane tape (9). Preliminary tests had shown that unlike skin, from which ink-stained stratum corneum is easily detached, ink marks are not transferred from the nail, which lacks this layer; however, the graphite particles left by a soft pencil were readily picked up by the tape. The proximal edge of clinically apparent infection was drawn on the affected nail with a soft pencil and the free edge of the nailfold was marked in ink; both marks were then transferred to paper with adhesive cellophane tape. The distance between the nailfold and the most proximal clinical involvement, projected to the midline of the nail, was measured using an ocular micrometer. We believe that this simple *transfer method* could be applied with advantage to measuring nail growth and disease, and their changes with treatment. The growth rate of the study nail was measured by making a transverse score in the midline with a blade, and measuring its distance from the nailfold, again using the tape *transfer method*, immediately and after 28 days.

RESULTS

All 8 patients completed 14 days' treatment with terbinafine without side effects, and were followed for 48 weeks. At the start of treatment the 8 patients had between them clinical

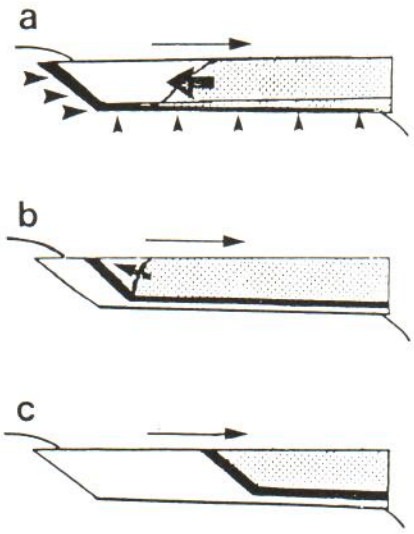

Fig. 1. Our original justification for short duration therapy which we based on an antifungal barrier zone moving from the matrix (4) and ventral nail (4) of an antifungal barrier zone: (*a*) the antifungal agent is incorporated during nail formation in the matrix of the root and ventral nail; (*b*) the band of antifungal activity is carried out with the growing nail, but the fungus can continue to grow proximally until it meets the drug; (*c*) the drug is a barrier to further fungal invasion, existing infection being carried out by nail growth.

infection of 25 fingernails and 62 toenails. At 24 weeks, 20 fingernails and 23 toenails previously involved were free of clinical infection; in nails still affected, the extent of nail involvement was reduced. All 8 patients showed clearance of one or more nail at 6 months, but in one patient a fingernail had become newly affected at 24 weeks. At 48 weeks, 1 further fingernail and 3 further toenails became clinically normal, but of nails normal at 24 weeks, 1 fingernail and 2 toenails had developed clinical infection.

By 4 weeks, mycological culture of *T. rubrum* proved negative in distal study nail clippings from 6 of the 8 patients, and in the remaining 2 patients was negative after 12 weeks. However, fungal hyphae continued to be demonstrated by microscopy of the clippings, in some cases until up to 36 weeks, despite continuing response. In one patient, cultures became negative, then were again positive from 12 weeks but without clinical relapse even at 48 weeks. In 2 patients who responded initially, cultures were negative at least twice but became consistently positive from 12 weeks and 36 weeks, respectively, and in both these cases there was clinical relapse. In a fourth, who showed no improvement in the study nail, negative cultures became positive after 36 weeks.

Arrest of fungal invasion as shown by outward movement of the diseased segment (Fig. 2) was apparent after 4 weeks in most patients, including in those nails in which the affected segment was more distal than proximal. With the exception of the patient who was receiving estrogen replacement therapy, the study nails showed a steady increase in unaffected nail length. In 3 study nails, outward movement continued until the affected segment grew out altogether, but in 2 initially responsive nails there was relapse after 16–20 weeks.

The growth rates of the study nails were measured in 7 of the patients and gave a mean of 67 μm per day (range 43–100) which was comparable to the mean rate of maximal outward movement of affected segments in the same nails of 68 μm/day (range 18–142); the mean difference between the two measurements for individual nails was 1 μm/day (95% confidence intervals 28 to -26 μm/day).

DISCUSSION

We found that a short course of treatment with terbinafine had an effect on fungal nail infection apparent after as little as 4 weeks; 80% of fingernails and 36% of toenails were cleared at 24 weeks. This was an open study on only 8 patients, but diagnosis and response, assessed clinically and by laboratory identification and growth of the fungus, were unequivocal, and the results cannot be attributed to spontaneous resolution.

Although the therapeutic effect of short-term treatment appeared to confirm our hypothesis, the measurements of the rate of response, for which we have used a novel transfer method, showed that our explanation was inadequate. We had expected that the fungus would continue to grow into the nail for 3–6 months, depending on the length of affected segment and the competing rates of nail and fungal growth, until it met the *cordon sanitaire* of antibiotic being carried out by nail growth. Only subsequently, as the fungus could no longer invade the nail, would the diseased segment be carried out, at the rate of growth of the nail. Instead, we found that the most proximal edge of clinical infection began to recede after only 4 weeks, and may have begun to do so even sooner; and thereafter regression of disease corresponded to the rate of outward growth of the nails.

The speed with which fungal growth ceased implies that the antibiotic reached the fungus more rapidly than predicted from the model of the movement of drugs in the nail (Fig. 1)

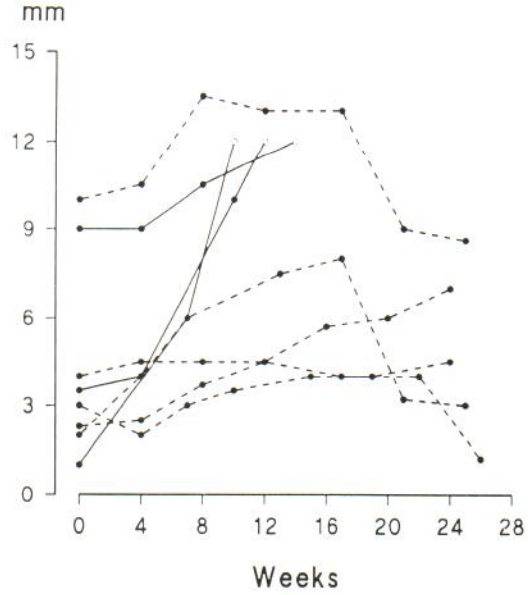

Fig. 2. Distance from nailfold to most proximal edge of diseased segment in study nails from the 8 patients treated with a short course of terbinafine. Fingernails are shown as solid lines and toenails as broken lines; open symbols represent the distance to free edge in nails which had become clinically normal. Outward movement of the affected segment is apparent from 4 weeks in all but one nail.

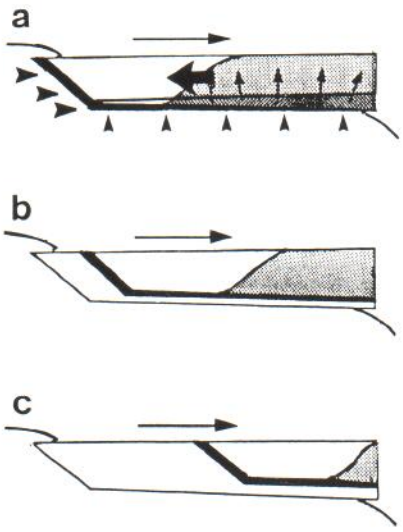

Fig. 3. New model to explain our finding of a rapid shunting of antibiotic to distal nail: (*a*) the antifungal agent is incorporated during nail formation as in Fig. 1, but reaches distal nail by diffusion from diseased ventral nail into overlying diseased nail plate; (*b, c*) fungal growth having been inhibited, there is no further spread of disease and the diseased segment is carried out with the growing nail. The drug persists in a band as in Fig. 1, growing out as a barrier to further fungal growth.

which we based on current beliefs. Likewise, the first mycological evidence of effect was found at 4 weeks after treatment, when distal nail clippings grew no fungus despite the continued presence of fungal filaments, confirming the ability of the drug to reach even distal nail at this time. It is unlikely that the drug could diffuse from the root through the normal nail plate to the site of distal disease. We therefore suggest that the drug reached this distal site by way of ventral nail growing from the nailbed under the site of fungal infection (Fig. 3). Movement of drug could then occur more easily into the crumble of the diseased nail.

Little is known about the kinetics of the entry and persistence of drugs into normal and diseased nail and it will now be important to establish how the antibiotic gains access into ventral as well as dorsal nail, what is its subsequent movement, and whether the rapid shunting into diseased distal nail occurs by transit through disordered ventral nail as we suggest. In this respect the relative involvement of ventral and dorsal nail and the anatomical preferences of the different fungi (10) could well prove important. (Since our study was completed, rapid appearance of terbinafine in distal nail has been reported (11), giving further support to our hypothesis.)

Our study was not designed for the study of therapeutic efficacy but to demonstrate that only a short exposure to antifungal therapy is necessary to obtain a detectable therapeutic response. In this respect the finding that improvement continued long after treatment stopped shows that the appearance of an affected nail alone cannot be used to assess therapeutic effectiveness. Thus an apparently poor response may be not so much a lack of the drug's effect as a consequence of slow outward growth of new nail, and does not in itself justify prolonged treatment. Similarly, the late relapse which occurred in some nails does not necessarily call for longer treatment, since relapse may indicate only the need for a higher initial dose to achieve adequate antifungal concentration.

Although fungicidal drugs such as terbinafine may have an advantage in preventing fungal regrowth beyond a zone of inhibition, we can see no reason why even fungistatic drugs such as griseofulvin and ketoconazole should not be effective in a short course, provided they persist in effective concentration in the nails; indeed we have found evidence for this possibility in early studies (3,12) although its significance was not appreciated at the time. Nevertheless, our results with a short course of treatment were as good as those obtained with conventional therapy with griseofulvin for months or years (1). To translate our conclusion into therapeutic practice will require studies on dose and duration for optimal response and relapse – including a single dose for each of several weeks.

In summary, we have established the new principle that a short course of an antifungal drug has a rapid and continued therapeutic effect on distal onychomycosis and that the use of regimens which last months or years owes more to tradition than to pharmacology. We therefore believe that the therapeutic goal of antifungal drug therapy should now be the use of a single dose.

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