

The Route of Rapid Access of Drugs to the Distal Nail Plate

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It has recently been shown that antimycotic drugs have unexpectedly rapid access to distal nail, which we have suggested occurs through the site of continuous ventral nail formation along the nail bed. To exclude the alternative possibility of diffusion through the nail plate, we have measured the effect of topical terbinafine cream in onychomycosis. Sustained outward movement of the fungally affected distal segment was seen in only 2 of 10 measured nails, and there was no change in the mean severity of clinical involvement in 53 nails under study. This excludes significant diffusion of drugs through the nail plate, and we conclude that the route of rapid access is indeed through the nail bed.

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By measuring the outward movement of diseased nail after a short oral course of the antimycotic terbinafine, we were able to show that the onset of the therapeutic effect on distal nail is rapid (1, 2). This demonstrated that drugs have rapid access to the distal nail and not, as previously believed (3), only by the slow outward movement of drug fixed during formation of nail in the germinal matrix. Others have since confirmed that terbinafine (4) and itraconazole (5) can be detected in distal nail clippings within a few weeks of starting oral therapy. We suggested that the route of rapid distal access was by the nail bed, recently shown to form ventral nail continuously along its length right up to the point of nail detachment (6, 7). However, we could not exclude the less likely possibility that drugs reached the distal nail by diffusion along the length of the plate from the zone of initial formation at the germinal matrix, or from surrounding skin. For this to occur, diffusion of terbinafine through the nail must be very rapid, and consequently we would expect this ready penetration through nail to allow a therapeutic effect as easily from topical application of the drug as from systemic administration. We have now tested this possibility.

PATIENTS AND METHODS

We studied 10 patients with clinically and microbiologically proven persistent distal subungual onychomycosis unresponsive to previous treatment with griseofulvin, because it was unlikely that the infection would regress spontaneously and it is well established that such resistant disease will nevertheless respond to terbinafine (8, 9). None had had griseofulvin within the previous 3 months and all had current positive fungal cultures from distal clippings. Only toenails were involved, and a total of 53 nails were affected in the 10 patients. Each patient was given 1% terbinafine cream, from which terbinafine is known to partition satisfactorily with the keratinocyte layer (10), to apply daily to the outer surface of each affected nail for 12 weeks. Four of the patients in whom onycholysis was marked were asked in addition

to apply the cream to the space underneath the nail. Assessments were made at the start, and after 2, 6, 12 and 24 weeks. In 4 of the patients further assessments were made for 12–24 weeks to exclude a continued response. For convenience of measurement, a single nail was chosen for study in each patient. At each visit the unaffected length of the study nail, between the nail fold and the most proximal clinically abnormal segment, was measured by the previously described transfer method (2). All nails were examined for clinical infection, and clinically graded on a 0–3 scale for each of onycholysis, hyperkeratosis and overall severity of involvement. Distal clippings for mycology were taken from the study nail.

RESULTS

Of the 10 patients, 8 showed no net outward movement of the affected segment of the study nail over the study period (Fig. 1). In 2 patients the study nails, both great toenails, showed continued outward growth and became normal by 48 weeks. The contralateral great toenails showed similar clinical improvement, but neither became completely normal. In all, of the original 53 affected nails only 3, all mildly affected, had become clinically normal at 24 weeks, and 2 more were now affected. The mean severity score of all affected nails was $4.6 \pm \text{s.d. } 1.9$ before treatment and 4.5 ± 1.6 at 24 weeks. There was no difference in the response of nails to which the terbinafine cream had been applied under the nails. The pathogen isolated from the study nail before treatment was *Trichophyton rubrum* in 9 patients and *T. interdigitale* in 1. Seven of the 10 study nails became culture negative by the end of treatment period of 12 weeks, although hyphae were still seen at microscopy in 4 of these, and 1 subsequently reverted to positive culture. The 2 study nails in which there was sustained reversal of fungal invasion first became culture negative at 2 and 36 weeks, respectively.

DISCUSSION

In 8 out of 10 patients we found no clinical improvement or outward movement of nail affected by fungal disease in response to 1% terbinafine applied topically to the outside of the nail plate and additionally to the underside in 4; there was sustained improvement in only 2.

All of the patients had clinically typical disease and the diagnosis was confirmed mycologically. After treatment fewer samples grew fungus, although filaments were still seen in some; these changes may simply reflect the continued presence of topically applied drug on the distal nail sample. Clinical improvement of study nails occurred in only 2 patients (one of whom applied the drug under the nail as well as to its surface), which suggests that diffusion of the drug through the nail from these sites is poor. Outward movement of the affected segment is a more sensitive and earlier indicator of therapeutic effect (2), but even with this method, we likewise failed to detect a response to 12 weeks' topical treatment in 8

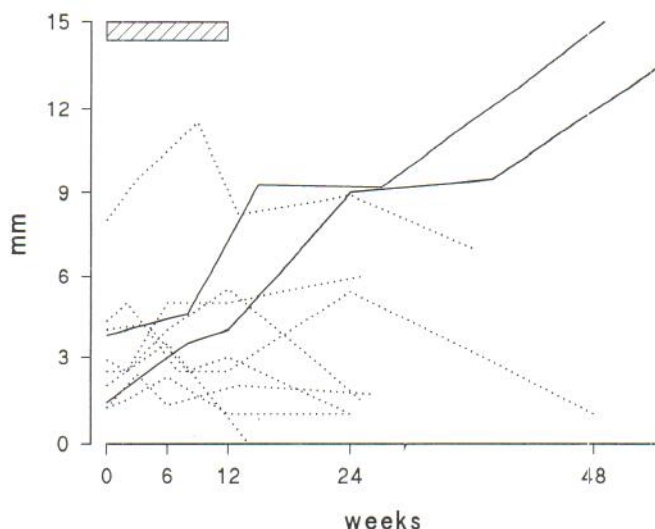


Fig. 1. Unaffected nail length in the nail under study in each of the 10 patients. Terbinafine was applied for 12 weeks (hatched box). Nails not showing possible improvement were not followed after 24 weeks; two great toenails which did show a sustained response are represented by solid lines.

of 10 patients. This finding contrasts with the results of a 2-week oral course of terbinafine, which produced a response in most patients, which was apparent as early as 4–6 weeks (2). Thus, despite this and other evidence that the drug can diffuse through nail (4) and that terbinafine cream partitions effectively with stratum corneum (10), the application of terbinafine cream onto the nail does not achieve therapeutic concentrations of the drug. It is possible that the outer surface of the nail is a greater barrier to diffusion than the rest of the nail, but in subjects who applied the cream under the edge of onycholytic nail, there was no clear added benefit. It follows that when terbinafine is given orally as a short course and rapidly reaches the site of distal nail disease, it cannot be doing so by rapid diffusion through the length of the nail plate from the site of its formation in the matrix, nor from the skin surface

at the nail margin. We therefore conclude that the route of rapid passage of drug to the distal nail is indeed as we have suggested (1, 2) from the nail bed, which contributes continuously to nail formation along its length (6, 7). Use of this route of access could allow the development of drugs for onychomycosis which require few, if not single, doses.

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