SYNOPSIS
Toenail onychomycosis in the United States is most often caused by the dermatophytes Trichophyton rubrum and T. mentagrophytes.

Topical treatments must penetrate the nail to reach the site of infection, but this may be inhibited by drugs binding to keratin within the nail.

Three topical antifungals have been approved by the United States Food and Drug Administration (FDA) for the treatment of onychomycosis, and there are many over-the-counter (OTC) topical antifungals that are used off-label for onychomycosis treatment.

OBJECTIVES

The objectives of these in vitro experiments was to evaluate the ability of commercially available topical antifungals to inhibit growth of T. rubrum and T. mentagrophytes via penetration of human cadaveric toenails and keratin-free cell cultures.

METHODS

Three prescription and four OTC topical antifungals were tested (Table 1).

Products were applied to human cadaveric toenails and allowed to dry prior to punching five 4-mm disks from the center of each nail; disks were placed in the center of an agar plate (85 mm radius) seeded with a clinical isolate of T. rubrum or T. mentagrophytes (two strains of each species were used; n=5 replicates for each product against each fungal strain) prior to incubation (5-7 days).

In a second experiment assessing antifungal activity in the absence of human nail, each product was applied to a 6-mm cellulose disk and placed on a seeded agar plate (n=3 replicates of each product against each strain prior to incubation (2-7 days)).

In both experiments, antifungal activity was assessed using zone of inhibition (ZOI), defined as the radius of the area of no fungal growth, disregarding any feathering; results were averaged across the two strains of each fungal species, and untreated cell cultures served as negative controls.

Differences in ZOI were analyzed using 2-tailed Tukey's post hoc test.

The threshold for significance was P<0.05.

RESULTS

In the cell culture penetration assay, average ZOIs for FDA-approved antifungals against both T. rubrum and T. mentagrophytes were greatest for efinaconazole; ZOIs for tolnaftate and ciclopirox were significantly lower (P<0.001, all).

Against both species, average ZOIs for all OTC products were similar to or less than for ciclopirox and significantly lower than for efinaconazole (P<0.001, all).

Among FDA-approved products, comparison of antifungal activity against both species via human nail penetration as a percentage of activity via disk diffusion demonstrated that efinaconazole > tavaborole > ciclopirox (Figure 3).

Overall, ZOIs were generally not associated with nail thickness (data not shown).

Representative images of fungal inhibition with FDA-approved antifungals are shown in Figure 4.

FIGURE 1. Fungal Inhibition via Penetration Through Human Cadaverous Toenail

TABLE 1. Antifungal Products Tested

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopirox</td>
<td>Ciclopirox 8% lacquer</td>
<td>Approved</td>
</tr>
<tr>
<td>Efinaconazole</td>
<td>Efinaconazole 10% solution</td>
<td>Approved</td>
</tr>
<tr>
<td>Tefinaconazole</td>
<td>Tefinaconazole 5% solution</td>
<td>Approved</td>
</tr>
<tr>
<td>Tolnaftate</td>
<td>Tolnaftate 1% solution</td>
<td>OTC</td>
</tr>
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<td>Tavaborole</td>
<td>Tavaborole 10% solution</td>
<td>OTC</td>
</tr>
<tr>
<td>Terpenicol</td>
<td>Terpenicol 1% solution</td>
<td>OTC</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Itraconazole 1% solution</td>
<td>OTC</td>
</tr>
</tbody>
</table>

In the cell culture diffusion assay, average ZOIs among FDA-approved antifungals were maximal (85 mm) against both species for efinaconazole and tavaborole; average ZOIs for ciclopirox were significantly lower (P<0.001, all).

Against both species, average ZOIs for all OTC products were similar to or less than for ciclopirox and significantly lower than for efinaconazole (P<0.001, all).

Among FDA-approved products, comparison of antifungal activity against both species via human nail penetration as a percentage of activity via disk diffusion demonstrated that efinaconazole > tavaborole > ciclopirox (Figure 3).

Overall, ZOIs were generally not associated with nail thickness (data not shown).

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FIGURE 2. Fungal Inhibition in the Cellulose Disk Diffusion Assay

CONCLUSIONS

Efinaconazole demonstrated superior transungual penetration compared to other FDA-approved topical antifungals for onychomycosis and all OTC topical antifungal products tested.

Efinaconazole and tavaborole demonstrated maximal antifungal activity against two strains each of T. rubrum and T. mentagrophytes in a cell culture diffusion assay, significantly greater than with ciclopirox and OTC antifungals.

However, when required to penetrate through human toenail, antifungal activity of efinaconazole was significantly greater than all other products tested.

The greater nail penetration and fungicidal activity of efinaconazole is likely due to its low keratin affinity relative to other topical antifungals.

REFERENCES


AUTHOR DISCLOSURES

Dr. Ali Elabbasi and Dr. Mahmoud Ghannoum have no conflicts of interest. Dr. Mahmoud Ghannoum has acted as consultant and speaker for Ortho Dermatologics. Bon E. Eltchoy has provided data research support to funding from Ortho Dermatologics. Dr. Mahmoud Ghannoum is an employee of Ortho Dermatologics.}

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