Understanding onychomycosis treatment: mechanisms of action and formulation
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Abstract:

Historically, the eradication of onychomycosis has been a frustrating and often unsuccessful endeavor. However, new understanding about the mechanisms of action of anti-fungal agents, the introduction of two new topical agents, and the drugs and devices now being investigated offer greatly improved options for current and future management of these infections. The mechanisms of action of systemic and topical antifungal agents and devices effective against the most common dermatophyte and nondermatophyte causes of onychomycosis are discussed.

Keywords
Ciclopirox; efinaconazole; fluconazole; itraconazole; laser therapy; onychomycosis; photodynamic therapy; tavaborole; terbinafine

Full Text:

The majority of onychomycosis cases in the United States are caused by a dermatophyte, most commonly, Trichophyton rubrum, also the most common cause of tinea pedis (commonly referred to as athlete's foot). (1) Less common causative organisms include other dermatophytes, nondermatophyte molds, and occasionally yeasts (Table). The medications used to treat these infections demonstrate different sensitivities, depending on the causative organism(s).

The purpose of this article is to review the agents and devices used to treat onychomycosis, describing their mechanisms of action.

Systemic Agents

Two classes of systemic agents commonly are used for the treatment of onychomycosis: azole antifungal agents--specifically, the triazoles fluconazole and itraconazole--and an agent from the allylamine class, terbinafine. Only itraconazole and terbinafine have received approval by the US Food and Drug Administration (FDA) for this indication. The most common adverse effects associated with the use of the systemic agents are headache and gastrointestinal symptoms (nausea, vomiting, and diarrhea). Transient mild to moderate elevations in serum aminotransferase have been seen with these medications, (2) and hepatotoxicity also has been reported, with rare hematologic effects. Before beginning treatment and after 1 month of therapy, laboratory studies are advisable--at least serum transaminases, but some clinicians also obtain a full liver profile and blood count.

Triazole Antifungal Agents--Fluconazole and Itraconazole

Triazole antifungal agents inhibit the fungal p450 enzyme 14 alpha-demethylase, which, in turn, blocks conversion of lanosterol to ergosterol and ultimately inhibits the essential production of ergosterol in fungal cell membranes. Ergosterol depletion causes growth-inhibiting disruption of these cell membranes. Triazole antifungal agents are considered fungistatic rather than fungicidal.

Fluconazole is FDA-approved for the treatment of superficial and systemic Candida albicans infections as well as cryptococcal meningitis; although it is not specifically indicated for onychomycosis, it has been widely studied and is commonly used to treat this infection.

Itraconazole has demonstrated effective minimum inhibitory concentration (MIC) in vitro activity against Trichophyton species, other less commonly associated causative organisms in onychomycosis (Aspergillus flavus and Aspergillus fumigatus), and several other fungal species that do not cause onychomycosis. Itraconazole is not effective against Fusarium spp, one of the most common nondermatophyte mold causes of onychomycosis, nor against the mold Scopulariopsis spp. Prolonged treatment with itraconazole may
result in resistance of some fungal organisms, and cross-resistance with other azole antifungal agents has been reported.

Terbinafine

Terbinafine inhibits ergosterol biosynthesis through inhibition of the enzyme squalene oxidase (rather than p450 and lanosterol-converting enzymes). Fungal cell death results primarily through cell membrane changes mediated by squalene instead of by ergosterol deficiency. (3) Terbinafine is considered fungicidal rather than fungistatic. In vivo and in vitro testing have demonstrated that terbinafine is highly effective against dermatophyte organisms, and may be effective against some azole-resistant strains of Candida albicans, as well as Candida parapsilosis.

Topical Antifungal Agents

Topical antifungal agents lack the systemic adverse effects or drug-drug interactions associated with fluconazole, itraconazole, and terbinafine, as described above, and generally feature a low incidence of serious local adverse effects. Historically, the main disadvantages of topical therapy were poor bioavailability--and, in turn, less efficacy compared to systemic agents--and the need for frequent debridement of the affected nails by a clinician and weekly removal of the lacquer by patients. Two newer topical agents, efinaconazole and tavaborole, have demonstrated improved efficacy compared with other topical agents and are not formulated as lacquers (thus, removal is not necessary).

Ciclopirox 8% Solution

Ciclopirox, a synthetic antifungal agent, has been available in the United States since 1996. It was the first topical medication approved by the FDA for the treatment of onychomycosis. Its mechanism of action is poorly understood. Leem and colleagues (4) investigated the activity of this agent against the yeast Saccharomyces cerevisiae and found that ciclopirox seemed to target proteins in the yeast that affected the replication and repair of DNA as well as cellular transport. These researchers proposed that ciclopirox inhibits cell growth and metabolism, possibly through several targets in the organism.

Efinaconazole

Efinaconazole is an azole antifungal agent, with a mechanism of action identical to that of the systemic triazole agents discussed above--ie, inhibition of 14-alpha demethylase, with resulting downstream disruption of fungal cell membranes. However, the systemic adverse effects that are problematic with itraconazole and fluconazole are not seen with this topical agent.

Efinaconazole shows in vitro activity against T. rubrum and Trichophyton mentagrophytes. No clinically significant evidence of drug resistance to efinaconazole has been observed.

In addition, efinaconazole has been shown to have low keratin affinity; Sugiura and colleagues (5) suggested that this property enhances efinaconazole’s nail penetration and contributes to its fungicidal activity. These investigators tested free-drug concentrations--in suspensions prepared from keratin samples--of efinaconazole, ciclopirox, and amorolfine (similar to ciclopirox, amorolfine is an agent in a lacquer formulation; amorolfine is not FDA-approved). The free-drug concentration of efinaconazole was 14.3%, compared to 0.7% for ciclopirox and 1.9% for amorolfine, respectively (P < 0.001). They also tested the penetrations of these three agents through full-thickness, T. rubrum-infected human nails. Efinaconazole’s fungicidal activity was comparable to that observed with amorolfine and superior to the fungicidal activity of ciclopirox. In another experiment in a guinea pig model with T. mentagrophytes onychomycosis, efinaconazole decreased the fungal burden significantly more than ciclopirox and amorolfine lacquers (P < 0.01). (5)

Tavaborole

Tavaborole represents a new class of boron-containing drugs; it is a low-molecular weight, water-soluble agent, formulated in a topical nail solution that retains antifungal properties in the presence of keratin. Its mechanism of action is thought to be through inhibition of the enzyme aminoacyl-transfer ribonucleic acid synthetase, which downstream inhibits fungal protein synthesis. Tavaborole is active against most strains of
T. rubrum and T. mentagrophytes, the two species most commonly found in onychomycosis. No resistance to tavaborole has been observed in studies involving repeated exposure of these organisms to the drug.

Lasers

Currently, a number of laser devices are FDA-approved for the treatment of onychomycosis. The first laser devices to be approved were the short-pulse neodymium:yttrium-aluminum-garnet (Nd:YAG) 1064 devices. The exact mechanism(s) of action of laser systems in the treatment of onychomycosis is still poorly understood. (6) Although thermal damage was considered a possible explanation for the fungistatic or fungicidal activity of lasers, it is clear from in vitro studies that the level of laser-generated heat that would be lethal to T. rubrum is much higher than would be tolerable to patients. (7) It is possible--and more likely--that exposure to lasers elicits an immunologic effect in the host, or that these devices induce denaturization of enzymes, which is important to sustain the function and growth of fungi; moreover, experiments involving direct laser exposure did not demonstrate inhibition of fungal activity or growth. (8)

Thus, at this point in time, the FDA-approved labeling on lasers notes only the indication of "temporary increase of clear nail in onychomycosis," and these devices are not considered to be sufficiently effective to warrant their use as first-line monotherapy for these infections. Future discoveries may alter this paradigm dramatically.

Photodynamic Therapy

Research by a number of investigators has demonstrated that photodynamic therapy (PDT) has promise in the treatment of onychomycosis. (9-11) The mechanism of action involves fungal absorption of a chemical, which is metabolized into a photosensitizer, followed by exposure to a specific wavelength light that results in subsequent reactive oxygen species and fungal death. (12-14)

PDT is not currently a practical option for widespread use in treating onychomycosis, and to date no PDT system has been FDA-approved for this indication. However, PDT may be considered when onychomycosis is chronic and is refractory to other therapies, especially when the infection involves fewer nails and less common and more resistant organisms, such as nondermatophyte molds. (15)

Penetration-Enhancing Methods

The cure rates—mycologic, clinical, and complete—achieved under the best conditions with currently available medications are still suboptimal. The main obstacle to better efficacy appears to be the mechanics of the nail plate itself, not drug resistance. The plate presents a formidable barrier to topical antifungal agents, limiting topical bioavailability.

A number of methods have been proposed and tested to improve penetration through the nail plate, and several appear promising. Low-level electrical current (iontophoresis) may increase the transport of topical antifungal agents through the nail plate to the nail bed and matrix. (16,17) Several devices are currently being studied in clinical trials.

Other researchers have investigated lasers—which are not particularly effective as primary monotherapy—to enhance the pharmacologic bioavailability of topical agents. (18) Borovoy and Tracy (19) proposed that fenestration—ie, creating "windows" through the nail plate—using a carbon dioxide laser may be useful to enhance topical antifungal penetration. More recently, Lim and colleagues (20) tested this hypothesis using a fractional carbon dioxide laser and antifungal cream in a pilot study of 24 patients. The investigators found a 92% clinical response and a 50% complete response (including complete mycologic cure). No recurrences of infection were seen in the responders 3 months after the last treatment. Indeed, this strategy is promising.

Conclusion

Clinicians can now offer several treatment options when discussing therapies for onychomycosis with the availability of two new FDA-approved topical agents—including a new antifungal class—and generic formulations of the most effective systemic drugs. In addition, promising and novel approaches are being tested that involve direct laser targeting of the onychomycotic nail and fungal organisms themselves, laser-enhancing penetration systems, and PDT. All of these treatment options have different mechanisms of
action, and through a better understanding of the different therapeutic approaches, the clinician will be able to target cases of onychomycosis with increasing specificity—and perhaps combine therapies as future information unfolds.

References


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**TABLE.** Onychomycosis Causative Organisms in the United States

<table>
<thead>
<tr>
<th>Dermatophytes</th>
<th>Yeasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Common</td>
<td>Trichophyton rubrum</td>
</tr>
<tr>
<td>Less Common</td>
<td>Trichophyton mentagrophytes</td>
</tr>
<tr>
<td>Least Common</td>
<td>Trichophyton tonsurans</td>
</tr>
<tr>
<td></td>
<td>Microsporum canis</td>
</tr>
<tr>
<td></td>
<td>Epidermophyton floccosum</td>
</tr>
<tr>
<td></td>
<td>Nondermatophyte Molds</td>
</tr>
</tbody>
</table>
Most Common  
Acremonium spp
Fusarium spp

Less Common  
Scopulariopsis spp

Least Common  
Scytalidium spp
Aspergillus versicolor
Aspergillus flavus
Aspergillus fumigatus
Aspergillus terreus


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