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PHARMACOLOGY AND PHARMACODYNAMICS OF ANTIFUNGAL AGENTS (P GUBBINS, SECTION EDITOR)

Antifungal Penetration into the Nail and New Topicals for Onychomycosis

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Abstract Onychomycosis is a common and difficult to treat infection, owing predominately to the limited penetration of topical drugs to the site of infection. Systemic drugs are not an option for all patients due to adverse events and drug-drug interactions. In this article, we review the nail penetration and clinical efficacy data of topical drugs, including older agents such as ciclopirox and amorolfine, as well as the newer agents, efinaconazole and tavaborole. Additionally, we describe some unresolved questions in the management of onychomycosis.

Keywords Onychomycosis · Efinaconazole · Tavaborole · Ciclopirox · Amorolfine · Antifungal agents · Fungal infections

Introduction

Onychomycosis is defined as the fungal infection of the toenails or fingernails [1]. It is estimated that onychomycosis accounts for 15–40 % of all nail infections, but true prevalence is difficult to estimate due to lack of large-scale epidemiological studies [1, 2]. Published guidelines recommend systemic treatment with terbinafine or itraconazole for most types of onychomycosis [1]. However, these antifungal agents are associated with potentially serious drug-drug interactions and toxicities, such as hepatic dysfunction, which limit the patient populations who can receive them. Topical therapy has historically not been effective because the nail plate is made of hard keratin and is hydrophilic, which limits penetration of lipophilic and high molecular weight drugs. One study showed that the concentration of a topically applied drug decreased 1000 times between outer layer and inner layer [3]. Combination therapy with both systemic and topical therapy is an option in patients not likely to respond to topical monotherapy [1]. This article will detail the nail penetration and monotherapy clinical data of two most commonly used historical topical treatments, amorolfine and ciclopirox, and that of two new topical therapies that have recently been approved, efinaconazole and tavaborole.

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Onychomycosis Trials Overview

Most phase III trials for topical antifungal agents against onychomycosis have a non-drug-containing vehicle as its control; there are few comparative trials of active antifungal agents. Unless otherwise specified in this review, the topical treatments were self-applied daily for 48 weeks. Additionally, unless otherwise noted, the primary outcome was complete cure, defined as a little to no (≤10 %) clinical involvement of the affected nail, plus mycologic cure, defined as a negative potassium hydroxide (KOH) preparation and negative fungal culture. Secondary outcomes included mycologic cure, clinical improvement, and assessment of adverse events. Table 1

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Table 1 Efficacy rates of topical antifungals for onychomycosis

	Amorolfine 5 % nail lacquer compared to 2 % nail lacquer with nail filing and clipping [8]	Ciclopirox 8 % nail lacquer compared to vehicle with nail filing and clipping [16]	Efinaconazole 10 % solution compared to vehicle [26••, 27]	Tavaborole 5 % solution compared to vehicle [33••]
Complete cure (clinical cure + mycologic cure)	38 % vs. 12 %	6.5 % vs. 0.9 % (study 1) 12 % vs. 0.9 % (study 2)	18.5 % vs. 4.7 % (pooled analysis)	6.5 % vs. 0.5 % (study 1) 9.1 % vs. 1.5 % (study 2)
Mycologic cure	60 % vs. 55 %	29 % vs. 11 % (study 1) 36 % vs. 9 % (study 2)	55.2 % vs. 16.8 % (study 1) 53.4 % vs. 16.9 % (study 2)	31.3 % vs. 7.2 % (study 1) 35.9 % vs. 12.2 % (study 2)

shows the complete cure and mycologic cure rates for each drug in its respective late-stage clinical trials.

Older Regimens

Amorolfine

Amorolfine is a morpholine derivative that exerts antifungal activity through inhibition of ergosterol synthesis at two levels in the fungal cell wall. This agent is active against dermatophytes, yeasts, some molds, and other pathogenic fungi [4]. Amorolfine is marketed throughout the world under various brand names for the topical nail treatment of onychomycosis. It is available in the form of a lacquer utilizing a water-insoluble transungual drug delivery system [5]. Concentrations of amorolfine increase from 5 to 27 % after evaporation of lacquer solvents [6]. Polak et al. studied the pharmacokinetics of amorolfine in human nails and observed that amorolfine exceeded the minimum inhibitory concentration (MIC) of most fungi causing onychomycosis as early as 24 h after application [7].

Lauharanta conducted a multicenter, randomized, double-blind, parallel design study to evaluate the efficacy and safety of amorolfine nail lacquer at two strengths—2 % vs. 5 %—applied once weekly [8]. Patients were randomly assigned to either the 2 % group or the 5 % group and were treated until complete cure or for 6 months. Study investigators assessed 100 patients with onychomycosis for clinical response and mycologic findings. 38 % of patients in the 5 % amorolfine group experienced cure while 32 % experienced improvement and 30 % experienced failure. Only 12 % of patients in the 2 % group experienced cure ($P = 0.008$). Three months after stopping therapy, cultures were negative in 55 % of cases in the 2 % group and 60 % of cases in the 5 % group. It is noteworthy that amorolfine nail lacquer is currently available in only the 5 % formulation.

An open-label, randomized, parallel-group study compared amorolfine 5 % nail lacquer applied once weekly versus twice weekly in patients with onychomycosis of the fingernails and/or toenails [9].Three hundred seventeen patients were included in the efficacy analyses. Assessment at 3 months after treatment completion showed the following results in the once weekly group: 45.6 % cure, 23.8 % improvement, and 30.6 % failure. In the twice weekly group, 51.8 % patients were cured while 21.7 % experienced improvement and 26.5 % failed treatment. The investigators also determined that the clinical response to amorolfine treatment was time-dependent with greater than 50 % patients experiencing cure or improvement at 3 months after initiation of treatment. These numbers increased to 75 % in the once weekly group and 77.1 % in the twice weekly group at 3 months after the end of treatment. Of note, published guidelines recommend dosing amorolfine either once or twice weekly, despite no significant difference in efficacy between the dosing frequencies [1].

Ciclopirox

Ciclopirox is an 8 % topical solution in the form of a nail lacquer, which is approved by the Food and Drug Administration (FDA) for treatment of mild-to-moderate onychomycosis of fingernails and toenails without lunula involvement due to *Trichophyton rubrum* [10]. Ciclopirox has activity against the dermatophytes typically responsible for onychomycosis and is thought to act by chelating polyvalent cations, which inhibits the enzymes responsible for the breakdown of fungal cell peroxides [10].

The ciclopirox nail lacquer has been formulated to enhance penetration of the active drug through the nail plate thereby increasing its effectiveness. A newer formulation that contains a water-soluble polymer, hydroxypropyl chitosan, has greater affinity for keratin and may also be used to treat the area around the infected nail [11]. After evaporation of solvents contained in the lacquer, ciclopirox concentration reaches 35 %, which provides a high concentration gradient for penetration into the nail [12]. One study of the standard 8 % nail lacquer formulation evaluated the in vitro penetration of ciclopirox in human fingernails and determined that the concentrations of ciclopirox exceeded the MIC for common fungal pathogens [13].

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A single center, randomized, open-label study compared the in vivo nail penetration of the water-soluble ciclopirox nail lacquer to a standard amorolfine lacquer and found that the water-soluble ciclopirox formulation had better nail penetration at days 15 and 25 compared to the amorolfine lacquer that served as a reference [14•]. Nail concentrations for ciclopirox were 2.82 ± 0.58 mcg/mg after 15 days and decreased by 34 % to 1.85 ± 0.31 mcg/mg on day 25 ($P = 0.077$). Nail concentrations for amorolfine were 0.64 ± 0.11 mcg/mg on day 15 and decreased by 80 % to 0.13 ± 0.03 mcg/mg on day 25 ($P = 0.0002$). Both amorolfine concentrations were below the MIC for *Candida parapsilosis* and minimally exceeded the MIC for *T. rubrum,* the two pathogens studied in this analysis. Efficiency coefficients were calculated as ratios between the drug recovered in the nail and the MIC for *T. rubrum* and *C. parapsilosis*. Ciclopirox hydrolacquer showed significant superiority over amorolfine at both 15 days ($P = 0.0008$) and 25 days ($P < 0.0001$) against *C. parapsilosis* and at 25 days against *T. rubrum* ($P = 0.0008$). Similar results were observed in a recent study by Monti et al. where the application of the ciclopirox hydrolacquer resulted in rapid nail penetration of the active drug and provided ciclopirox concentrations that sufficiently inhibited fungal growth for 7 days after the application [15•].

Gupta et al. conducted two identical double-blind, vehicle-controlled, parallel group, multicenter studies in the USA to evaluate the use of ciclopirox in adults with mild-to-moderate distal subungual tinea unguium of at least one great toenail with dermatophyte infection confirmed by both a positive KOH preparation and a positive dermatophyte culture [16]. Clinic evaluations occurred every 4 weeks. Drug application was on all toenails regardless of involvement and any affected fingernails. Every 7 days, the patients removed the nail lacquer using isopropyl alcohol swabs. Secondary outcomes included treatment cure defined as simultaneous negative KOH and culture and a global evaluation score of "cleared," mycologic cure, and negative mycologic culture.

A total of 460 patients were randomized in the two studies, half received ciclopirox [16]. At 48 weeks (end of treatment), ciclopirox-treated patients had significant improvement compared to vehicle-treated patients. Treatment success was 6.5 % vs. 0.9 % ($P = 0.031$, study 1) and 12 % vs. 0.9 % ($P = 0.001$, study 2). Mycologic cure rates were higher in the ciclopirox group: 29 % versus 11 % ($P = 0.002$) and 36 % vs. 9 % ($P < 0.001$), in each study, respectively. Significant improvement in mycologic outcomes was seen as early as 12 weeks into the study period. Ciclopirox-treated patients also achieved a higher rate of treatment cure in both studies: 5.5 % vs. 0.9 % ($P = 0.059$, study 1) and 8.5 % vs. 0 % ($P = 0.001$, study 2). Patients who achieved treatment cure were eligible for an additional 12 weeks of follow-up. Seven out of 12 patients who were followed beyond 48 weeks remained cured while four of 12 did not. The one remaining patient achieved negative mycology and was described to have nearly clear nails. Non-serious adverse events were reported in both ciclopirox and vehicle groups and included application site reactions, changes in nail shape or color, and localized erythema.

Ciclopirox was studied in a multicenter, randomized, controlled trial comparing debridement alone every 3 months to debridement every 3 months plus ciclopirox daily for 9–12 months as combination treatment for pedal onychomycosis [17]. Median follow-up time was 10.5 months. The primary outcome of this study was the presence or absence of fungi on final culture with or without positive fungal microscopy viewed with periodic acid-Schiff (PAS) staining. Seventy-seven percent of patients in the ciclopirox plus debridement group achieved mycologic cure compared to 0 % in the debridement only group.

Another multicenter, prospective, randomized, controlled trial evaluated the efficacy and safety of a novel formulation of ciclopirox 8 % hydrolacquer (P-3051) compared to the marketed ciclopirox 8 % nail lacquer formulation in patients with mild-to-moderate distal subungual onychomycosis of at least one big toenail [18]. Patients were randomized to receive P-3051 ($n = 182$), the reference drug ($n = 188$), or placebo ($n = 97$). This treatment period was followed by a 4-week washout period and additional 8 weeks of follow-up. Efficacy variables of the target nail included KOH microscopy, fungal culture, and the percentage of infected nail area on the total nail surface. Complete cure after 48 weeks was significantly higher in patients who received P-3051 compared to placebo vehicle (5.7 % vs. 0 %, respectively, $P = 0.0165$) but not superior or significantly different when compared to the reference ciclopirox. At 60 weeks, the ciclopirox hydrolacquer (P-3051) group had 12.7 % complete cure, which was higher than the 5.8 % complete cure rate in the reference group ($P < 0.05$) and 1.3 % in the placebo group ($P = 0.0029$).

New Regimens

While the use of amorolfine and ciclopirox monotherapy may be effective for some patients, the efficacy rates are not optimal. Alternative dosing schemes of both agents have been tested without significant improvement [9, 19, 20]. Additionally, other drugs, such as terbinafine, have been studied as a topical formulation with limited efficacy [21]. Therefore, additional new agents, ideally with enhanced nail penetration, have been sought for topical monotherapy. Recently, efinaconazole and tavaborole gained regulatory approval for this indication.

Efinaconazole

Efinaconazole is a topical azole antifungal 10 % solution that works by inhibiting fungal lanosterol 14α-demethylase,

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which prevents formation of ergosterol [22]. Efinaconazole has shown similar or increased potency against common onychomycosis-causing fungi, including *T. rubrum*, *Trichophyton mentagrophytes*, and *Candida albicans*, compared to other marketed onychomycosis treatments [23]. Efinaconazole has been shown to have lower affinity to keratin than ciclopirox and amorolfine ($P<0.001$ for each comparison), leading to higher free drug concentrations [24•]. Additionally, efinaconazole produced a region of fungal growth inhibition under the nail in an in vitro study, where neither ciclopirox nor amorolfine did [24•]. When tested in an in vivo guinea pig model, the viable fungal cell counts were significantly lower in those treated with efinaconazole than those treated with either ciclopirox or amorolfine ($P<0.01$ and $P<0.001$, respectively) [24•]. A separate analysis in a cadaver nail model indicated that efinaconazole's nail penetration does not seem to be negatively impacted by the presence of nail polish, unlike other topical products [25].

The clinical efficacy of efinaconazole was evaluated in two identical phase III multicenter, randomized, parallel-group, double-blind, vehicle-controlled studies in patients with mild to moderate toenail onychomycosis [26••]. Patients received either efinaconazole or vehicle without nail debridement with a 4-week intervention-free follow-up period. Efficacy and safety evaluations were completed at baseline, at 12-week intervals during treatment, and then at end of follow-up period.

One thousand six hundred fifty-five patients were randomized at 118 sites in the USA, Canada, and Japan [26••]. The pooled study primary endpoint results showed significant differences in complete cure rates between efinaconazole and vehicle-treated patients (18.5 % vs. 4.7 %, $P<0.001$), and the difference became statistically significant from week 36 onwards [27]. Significant differences were also seen between efinaconazole and vehicle-treated patients for mycologic cure (55.2 % vs. 16.8 %, respectively, in study 1, 53.4 % vs. 16.9 %, respectively, in study 2, $P<0.001$ for both) and complete or almost complete cure (26.4 % vs. 7 %, respectively, in study 1, 23.4 % vs. 7.5 %, respectively, in study 2, $P<0.001$ for both) [26••]. A subgroup analysis demonstrated that females had higher complete cure rates than males (27.1 % vs. 15.8 %, respectively, $P=0.001$), and patients with mild disease had higher complete cure rates than those with moderate disease (24.2 % vs. 14.5 %, respectively, $P<0.001$) [27]. A post hoc analysis showed that patients in the phase III trials who had at least 10 % improvement in the affected nail by week 12 of treatment and those who had mycologic cure by week 24 were more likely to achieve complete cure [28]. In another post hoc analysis, patients in the phase III trials coinfected with tinea pedis had higher complete cure rates and mycologic cure rates when the tinea pedis was treated simultaneously compared to those in whom the tinea pedis was not treated simultaneously [29].

Overall, efinaconazole adverse events were similar to vehicle (66 % vs. 61 %, respectively, in study 1, 64.5 % vs. 58.5 %, respectively, in study 2) and generally mild or moderate in nature, not related to study drug, and resolved without complications. While the rate of discontinuation as a result of adverse events was higher for those receiving efinaconazole than vehicle (3.2 % vs. 0.5 %, respectively, in study 1, 1.9 % vs. 0 %, respectively, in study 2) and the most common adverse events leading to discontinuation were application site dermatitis and vesicles, other localized skin reactions were similar to vehicle [26••].

Tavaborole

Tavaborole is a topical oxaborole antifungal 5 % solution with a novel mechanism of action of inhibiting an aminoacyl-transfer ribonucleic acid synthetase, thereby preventing fungal protein synthesis [30]. In vitro, tavaborole showed similar or lower minimum inhibitory concentrations (MICs) to a wide range of fungi, including *T. rubrum*, *T. mentagrophytes*, and *C. albicans*, when compared with ciclopirox, terbinafine, fluconazole, and itraconazole [31•]. Additionally, the MIC of *T. rubrum* to tavaborole was not significantly altered in the presence of keratin, indicating possible enhanced nail penetration [31•]. Tavaborole showed higher concentrations in the ventral/intermediate nail layer compared to ciclopirox after 14 days of treatment ($P=0.003$), and tavaborole nail penetration was 40-fold greater than that of ciclopirox after 14 days of treatment ($P<0.004$) [31•]. Tavaborole also produced a region of fungal growth inhibition under the nail in an ex vivo study, where neither ciclopirox nor amorolfine did [31•]. A separate ex vivo analysis indicated that tavaborole's nail penetration does not seem to be negatively impacted by the presence of nail polish [32].

The clinical efficacy of tavaborole was studied in two identical phase III, multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials in patients with mild to moderate toenail onychomycosis [33••]. Patients received either tavaborole or vehicle without nail debridement with a 4-week treatment-free follow-up period. Efficacy and safety evaluations were made at baseline, week 2, week 6, and every 6 weeks thereafter. The primary efficacy outcome was complete cure at week 52. Secondary efficacy endpoints included completely or almost clear affected nail, negative mycology, and completely or almost clear nail plus negative mycology. Completely clear nail was defined as no clinical evidence of onychomycosis, no onycholysis, and no subungual hyperkeratosis. Almost clear nail was defined as no more than minimal evidence of onychomycosis (≤10 % toenail plate that was dystrophic or discolored) with minimal onycholysis and subungual hyperkeratosis.

One thousand one hundred ninety-eight patients were randomized at 59 sites in the USA, Canada, and Mexico

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[33••]. Patients who received tavaborole had a significantly higher complete cure rate than those receiving vehicle (6.5 % vs. 0.5 %, respectively, in study 1, $P=0.001$; 9.1 % vs. 1.5 %, respectively, in study 2, $P<0.001$). Significant differences were also seen in completely or almost clear nail at week 52 (26.1 % vs. 9.3 %, respectively, in study 1, 27.5 % vs. 14.6 %, respectively, in study 2; $P<0.001$ for both) and negative mycology (31.3 % vs. 7.2 %, respectively, in study 1, 35.9 % vs. 12.2 %, respectively, in study 2; $P<0.001$ for both).

Overall, tavaborole treatment-emergent adverse events were similar to vehicle (64.4 % vs. 69.9 %, respectively, in study 1, 57.5 % vs. 54 %, respectively, in study 2), generally mild or moderate in nature, and not related or unlikely related to study drug [33••]. Treatment-related treatment-emergent adverse events were more common with tavaborole than vehicle (8.8 % vs. 2.6 %, respectively, in study 1, 3.3 % vs. 0.5 %, respectively, in study 2), mostly due to application site reactions. The most common treatment-related application site adverse events were exfoliation (2.7 %), erythema (1.6 %), and dermatitis (1.3 %). Rates of discontinuation due to adverse events were similar regardless of treatment group (0.3—1 %).

Conclusions

One of the biggest challenges for onychomycosis treatment is reaching the site of infection. In vitro, efinaconazole and tavaborole appear to penetrate the toenail plate better than other topical treatment options. While efinaconazole and tavaborole are attractive additions to the onychomycosis armamentarium, complete cure and mycologic cure rates are still not optimal with these agents, with less than 20 % of patients in phase III trials achieving complete cure. Some additional questions remain with the use of efinaconazole and tavaborole, including if they can be used in patients with severe disease, as this is a patient population excluded from the phase III trials. The phase III studies only looked at 48-week treatment durations with a 4-week follow-up period, so the impact of longer treatment durations on outcomes, safety, and resistance, as well as the outcomes at time points after follow-up ended remain unknown. The question of whether combining one of these topical agents with debridement or systemic therapy would improve outcomes is yet to be answered. Further studies will be required to answer these clinically important questions. Finally, further drug discovery trials are needed to determine if there are additional antifungal agents, systemic or topical, which would provide higher rates of complete and mycologic cure without significant adverse events or drug-drug interactions for this complicated to treat disease.

Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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