Advancements in Topical Antifungal Vehicles

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ABSTRACT

The primary treatment for superficial fungal infections is antifungal topical formulations, and allylamines and azoles represent the two major classes of topical formulations that are used to treat these infections. The stratum corneum (SC) is composed of keratinocytes that are surrounded by a matrix of lipids. The efficacy of topically applied formulations depends on their ability to penetrate this lipid matrix, and the vehicle plays an integral role in the penetration of active molecule into skin. There are several challenges to formulating topical drugs, which include the biotransformation of the active molecules as they pass through the SC and the physical changes that occur to the vehicle itself when it is applied to the skin. This article will review current and emerging topical antifungal vehicles.

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INTRODUCTION

Superficial cutaneous fungal infections (SCFIs) are commonly encountered in clinical practice in the United States, and comprise infections of the skin by dermatophytes and yeasts.[1-3] Although SCFIs are seldom life threatening, they can severely affect patients' quality of life.[1-3] The most common of the SCFIs are dermatophyte infections, which result from fungi and affect the keratinized tissues of the skin, hair, and nails.

The primary treatment for SCFIs is antifungal topical formulations.[4-5] Allylamines and azoles represent the two major classes of topical formulations that are used to treat SCFIs.[4,5] Although both classes of topical formulations are clinically effective, allylamines have fungicidal activity against dermatophytes.[4,5] Conversely, the azoles are known to have greater activity against yeasts such as Candida spp and Malassezia spp, but topical allylamines have also shown to be efficacious for cutaneous candidiasis.[4,5]

Allylamines inhibit squalene epoxidase, which is a vital enzyme in the ergosterol biosynthesis pathway of fungal cell membrane formation.[6] The subsequent alterations in the fungal cell membrane formation results in cellular permeability and growth inhibition.[6] The allylamine antifungal agents in clinical use include naftifine, butenafine, and terbinafine.[6]

Azole antifungals also inhibit the synthesis of ergosterol by inhibiting the enzyme 14 alpha demethylase and thus disrupting the fungal cell membrane.[6] The azole antifungal agents in clinical use contain either two or three nitrogens in the azole ring and are classified as imidazoles (eg, ketoconazole and miconazole, clotrimazole) or triazoles (eg, itraconazole and fluconazole).[6]

A meta-analysis conducted by Rotta et al evaluated the efficacy of topical antifungals used in dermatophytosis treatment.[7] The investigators performed a comprehensive search for randomized, controlled trials comparing topical antifungals with one another or with placebo in dermatophytosis treatment through July 31, 2012 for all entries in MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Literatura Latino Americana e do Caribe em Ciências da Saúde, and International Pharmaceutical Abstracts.[7] The investigators concluded that there was not a statistically significant difference among the outcomes regarding mycologic cure rates at the end of treatment among the various antifungals, but the allylamines naftifine, butenafine, and terbinafine are possibly the best strategies for maintaining a cured status among patients.[7]

Although all of the Food and Drug Administration (FDA) approved antifungals prescribed today produce mycologic cure rates, a primary difficulty for antifungal topical drug delivery is the low diffusion rate of drugs across the stratum corneum (SC).[8] The SC is composed of keratinocytes that are surrounded by a matrix of lipids. The efficacy of topically applied formulations depends on their ability to penetrate the lipid matrix of the SC.[9,10] The primary lipids found in the stratum corneum are phospholipids, cholesterol-3-sulphate, cholesterol, ceramides, sterol esters, and free fatty acids. The sebaceous lipids in the SC include triglycerides, wax esters, and squalene. [9,10]

In the topical administration of antifungals, the active drug should pass the SC, particularly into the viable epidermis. Consequently, the vehicle plays an integral role in the penetration of the active molecule into skin and ultimate clinical efficacy.[11] Depending on the properties of the delivery vehicle, the penetration of the active drug can be quite variable.[12] For example,

the potency of topical corticosteroids has been evaluated by vasoconstrictor assay, and the same concentration of a topical corticosteroid can have potency that varies significantly in different vehicles.[13]

Vehicles contain a myriad of different chemicals, and there are several challenges to formulating topical drugs, which include the biotransformation of the active molecules as they pass through the SC and the physical changes that occur to the vehicle itself when it is applied to the skin.[14,15] Vehicles generally include ingredients that disrupt the skin barrier as they fluidize the lipid channels between corneocytes and transport the active drug into the cutaneous structures.[14] Detergents and emulsifiers are often used as vehicle excipients, because they disrupt and penetrate the SC. Propylene glycol is probably the most common excipient in topical vehicles, because it has multifunctional properties that act as a solvent, humectant, penetration enhancer, in addition to antimicrobial characteristics. At high concentrations, propylene glycol induces desquamation, which widens the cellular pathways and also disrupts the epidermal barrier.

Topical delivery systems often have a rheologic agent that improves its spreadability.[16] Microorganisms can form and proliferate in the water phase of a topical product, so topical formulations regularly include preservatives.[16] Fragrance or coloring agents may also be incorporated into a vehicle to modify the cosmetic features of the product. The relationship of these various ingredients will determine the efficacy of the final product.[16]

For decades, dermatologists have relied on creams and ointments for the topical treatment of SCFIs, but patient dissatisfaction with these delivery vehicles can result in reduced patient compliance and exacerbate SCFIs. Consequently, newer delivery vehicles in dermatology have been developed to improve clinical efficacy, reduce adverse events such as irritation, and enhance patient adherence. The newer vehicles include gels and foams, which often provide better application properties, adherence, and patient satisfaction in comparison to traditional vehicles. In addition to the ease of spreadability, particularly in hair bearing areas, gels and foams are particularly well suited for application over larger areas.

Current and Emerging Antifungal Vehicles

Naftifine hydrochloride gel and cream, a topical allylamine, is a fungicidal that has shown to be efficacious against a wide spectrum of dermatophyte.[17,18,19, 20,21] The active ingredient of naftifine gel and cream is naftifine hydrochloride. The gel vehicle contains alcohol, benzyl alcohol, edentate disodium, hydroxyethyl cellulose, purified water, propylene glycol, polysorbate 20 and trolamine.[22] Propylene glycol acts as its primary penetration enhancer. The cream vehicle contains benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sosium hydroxide, sorbitan monostearate, stearyl alcohol, and hydrochloric acid.[23] In this case, isopropyl myristate is the major penetration enhancer.

Naftifine inhibits squalene epoxidase, thus inhibiting the conversion of squalene to squalene epoxide in ergosterol biosynthesis. Naftifine has potent in vitro fungicidal activity against dermatophytes, which correlates with its clinical and mycological activity in patients with dermatophytosis, as well as some anti inflammatory properties.[19] Naftifine application has also demonstrated a significant improvement in clinical symptoms and therapeutic success after courses of therapy between 2 to 6 weeks in a high percentage of patients with interdigital tinea pedis, tinea cruris, or corporis.[17,18,9]

> "The efficacy of topically applied formulations depends on their ability to penetrate the lipid matrix of the SC."

Naftifine gel 2% is approved for the topical treatment of interdigital tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum in patients 18 years of age or older.[22] Naftifine cream 2 % is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by Trichophyton rubrum in patients 18 years of age or older.[23] Both treatment regimens are applied topically once daily for two weeks in clinical studies. However, post-treatment improvement has been seen for up to two weeks in the case of tinea cruris and up to four weeks in the case of interdigital tinea pedis.[17,18] Similar trends in post-treatment improvement for up to four weeks after treatment cessation have also been demonstrated using naftifine gel 2% in subjects with interdigital type tinea pedis with or without moccasin-type infection.[17,24]

Plaum et al conducted an open-label, single-exposure study that tested the hypothesis that one of the reasons for the efficacy of naftifine 2% cream or gel is that drug-levels remained in the SC after the cessation of therapy.[20] The investigators utilized a tape stripping methodology to assess the amount of drug available in the SC over a 28-day period following the cream or gel's last application.[20] Six subjects were given naftifine cream 2% and six subjects were given naftifine gel 2%. The 12 subjects had twelve application sites on their upper backs, and 11 of the sites were dosed with one of the test formulations for 14 days. The final site remained untreated to serve as the control site.[20]

On days 15, 29, and 43, a selected test site was tape stripped to glean cells from the SC. The tape strips enabled the investigators

to quantify the amount of drug present on the subjects' backs.[20] Plaum et al found that naftifine was present on all tape strip samples collected over the 28-day period after the cream or gel's initial application.[20] Moreover, the most relevant, deeper tape strip sets showed the potentially clinically relevant presence of naftifine in the skin 28 days post-treatment.[20] The investigators' findings elucidate the progressive improvement in clinical and mycological response rates not only during the treatment period but also for up to four weeks post-treatment using naftifine cream or gel.[20]

Kircik and Onumah conducted an 8-week pilot study that examined the efficacy of naftifine hydrochloride cream 2% and urea cream 39% for the treatment of tinea pedis with hyperkeratosis.[21] The treatment of tinea pedis with hyperkeratosis has traditionally been difficult for dermatologists due to the presence of thick scaling after the resolution of the active fungal infection. So the investigators utilized urea, because it is a keratolytic agent that clears the skin of hyperkeratosis scaling.[21]The investigators followed 10 patients for 8 weeks.[21] At baseline, the subjects were given a 2-week supply of naftifine hydrochloride cream 2% and an 8-week supply of urea cream 39%.[21] At weeks, 2, 4, and 8, the subjects were evaluated for compliance, and they also completed a visual analog scale (VAS) for pruritus severity and a dermatology life quality index (DLQI) questionnaire in addition to verbal and clinical assessments.[21] At week 8, Kircik and Onumah recorded significant clinical improvements and also subject satisfaction.[21] Over the 8-week period, the subjects had a 1-point improvement in the resolution of their hyperkeratosis.[21] Moreover, the subjects experienced a statistically significant median 2-point improvement in VAS pruritus severity, and a median 3-point improvement over the 8 weeks in their DLQI from baseline.[21] The investigators concluded that naftifine hydrochloride cream 2% and urea cream 39% were effective for the treatment of tinea pedis with hyperkeratosis, because, in part, the urea cream mitigated hyperkeratotic scaling, which facilitated the penetration of naftifine hydrochloride.

A 2014 study, conducted by Erdal et al, assessed the absorption of another, allylamine , terbinafine in a gel formulation in the presence and absence of three chemical enhancers: nerolidol, dl-limonene, and urea.[25] The investigators applied terbinafine 1% to the SC of healthy subjects, and, after 8 hours, used tape stripping and ATR-FTIR spectroscopy to determine absorption rates.[25] Erdal et al found that the terbinafine gel formulation containing nerolidol produced significantly greater terbinafine permeation through the SC than formulations containing urea and dl-limonene.[25] ATR-FTIR spectroscopy demonstrated that the terbinafine gel formulation containing nerolidol induced lipid bilayer disruption in the SC.[25]The formulation with urea produced enhanced permeation of terbinafine into the SC, whereas dl-limonene produced a relatively minimal accumulation of terbinafine in the upper SC.[25] Erdal et al concluded that a terbinafine gel formulation with nerolidol could potentially be of benefit for both superficial and deep cutaneous fungal infections.[25]

A study published in 2015, conducted by Pillai et al, assessed various formulations of butenafine hydrochloride gel, and their affects on ex vivo skin permeation and antifungal activity when compared to marketed butenafine hydrochloride cream.[26] The investigators incorporated isopropyl palmitate for the oil phase, and aerosol OT and sorbitan monooleate as surfactants.[26] They found that incorporating the aforementioned ingredients into Carbopol 940 gel had greater efficacy when compared to sodium alginate or hydroxyl propyl methyl cellulose gels. Pillai et al concluded that the developed gel demonstrated superior ex vivo skin permeation and antifungal activity when compared to marketed butenafine hydrochloride cream.[26]

Several studies have evaluated the safety and efficacy of a formulation of luliconazole cream 1%, which contains benzyl alcohol, butylated hydroxytoluene, cetostearyl alcohol, isopropyl myristate, medium-chain triglycerides methylparaben, polysorbate 60, propylene glycol, purified water, and sorbitan monostearate. Benzyl alchohol, propylene glycol, and isopropyl myristate act as the vehicle's primary penetration enhancers. In the preclinical guinea pig studies, high levels of luliconazole were achieved in the stratum corneum of guinea pig plantar skin within three consecutive days of application and was maintained over 14 days of application.[27]

A phase III randomized, double-blind, vehicle-controlled study assessed the safety and efficacy of luliconazole cream 1% in subjects with tinea pedis who were 12 years of and older.[28]The study included 321 patients; 159 subjects were randomized to receive luliconazole cream 1% and 162 received the vehicle once daily for 14 days.[28]The efficacy of luliconazole cream 1% regarding erythema, scaling, pruritus and mycology was evaluated at days 28 and 42, which were 14 and 28 days post-treatment.[28] On day 42, investigators found that 26.4% of subjects receiving luliconazole cream 1% achieved a complete clearance of clinical signs and mycology, and 1.9% of patients treated with the vehicle achieved a complete clearance of clinical signs and mycology ($P< 0.001$)[28]Comparable safety profiles were also recorded for luliconazole cream and the vehicle.

Sertaconazole has shown efficacious antifungal activity against dermatophytes that may have reduced susceptibility to other azoles. Susilo et al conducted a study to assess the rate and extent of the penetration of sertaconazole nitrate 2% cream into the SC.[29] The study included 12 healthy volunteers who were exposed to 8 applications of sertaconazole nitrate 2% cream or placebo over time intervals ranging between 0 and 48 hours.[29] The investigators used tape stripping and an HPLC-assay to determine the penetration of sertaconazole into three layers of the

epidermis. Sertaconazole nitrate cream penetrated the SC shortly after application, and a relevant amount of the applied dose was recovered from the SC within 30 minutes after its initial application.[29] A plateau of sertaconazole was achieved three hours after administration, and it was maintained for 48 hours.[29]The estimated average level of sertaconazole nitrate penetration of the SC following the application of 100 milligrams of the cream was 1409 micrograms immediately after application, and it plateaued to 9029 micrograms at 3 hours.[29]The relative proportion of sertaconazole penetrating the SC was 1% at 12 hours, 34.2% at 24 hours, and 37.6% after 48 hours.[29] Susilo et al concluded that the rapid penetration of sertaconazole nitrate cream into SC and its increasing penetration over time, without significant quantities being distributed into blood, made it a favorable antifungal preparation.[29]

In 2014, the FDA approved econazole nitrate 1% foam for the treatment of interdigital tinea pedis. Econazole nitrate 1% foam incorporates patented Proderm Technology®, which is a water-lipid based dermal delivery technology that has demonstrated the potential to repair and restore compromised skin barrier function while delivering active ingredients without disrupting skin barrier function.[30,31] To assess the safety and efficacy of econazole nitrate 1% foam compared to the foam vehicle for the treatment of interdigital tinea pedis, Elewski and Vlahovic conducted two randomized, double-blind, parallel-group, vehicle-controlled, multicenter trials.[31]The trials enrolled males and females ≥12 years old with a clinical diagnosis of interdigital tinea pedis who also had a baseline fungal culture that was positive for a dermatophyte.[31] The trials' subjects applied econazole nitrate 1%foam (n=246) or the foam vehicle (n=249) once daily for 4 weeks.[31]The trails' primary endpoint was the percentage of subjects achieving a complete cure, which included a negative KOH, negative fungal culture, and a complete resolution of all signs and symptoms at 2 weeks post-treatment or day 43.[31] Elewski and Vlahovic found that the complete cure rate by day 43 was 24.3% for the subjects receiving econazole nitrate foam compared to 3.6% for the subjects receiving the foam vehicle.[31] The investigators determined that econazole nitrate foam was highly efficacious over the foam vehicle for the primary and secondary endpoints, and it was safe and well tolerated with a safety profile similar to the foam vehicle.[31]

CONCLUSION

Topical anti-fungal treatment for SCFIs is a primary component of the dermatologic armamentarium, and effective treatment of SCFIs depends on both the active drug and the vehicle. The efficacy of topical formulations for SCFIs is not exclusively contingent on the concentration of the active drug but also the vehicle which plays an integral role in the success of topical treatment. Depending on the vehicle, penetration of the active drug can be quite variable. In addition to enhancing an anti-fungal's effectiveness, a vehicle may itself cause adverse effects, so the development of a vehicle includes multiple considerations. A myriad of diverse and molecularly complex classes of new topical vehicles are continuously being studied and refined in dermatologic research arena.

In this review of topical antifungal vehicles, we found that certain vehicles enhances efficacy up to four weeks post treatment by enabling the retention of the active molecule in the stratum corneum as in the case of naftifine cream and gel. The depo effect in stratum corneum of naftifine or similar agents shortens the treatment period, which increases patient compliance. Additionally, certain properties of vehicles such as ease of use, increase spreadability, and tolerability with a moisturizing effect in case of econazole foam, also increase patient compliance hence efficacy. Thus, we can not emphasize enough the importance of vehicles not only in topical anti fungal treatment but also in all aspects of topical dermatologic therapy.

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