Butenafine: An Update of Its Use in Superficial Mycoses

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ABSTRACT

Butenafine is a synthetic benzylamine antifungal agent that may be fungicidal against susceptible organisms, e.g., dermatophytes. Butenafine may be effective and safe in the treatment of interdigital tinea pedis (apply twice daily for 1 week or once daily for 4 weeks), tinea corporis/ tinea cruris (apply twice daily for 2 weeks), and pityriasis versicolor (apply once daily for two weeks). The effectiveness of the drug persists for at least 4 weeks following the discontinuation of therapy suggesting that there is some retention of the drug in the skin following termination of active therapy.

Key words: butenafine, tinea, fungal

Topical butenafine (Mentax®, Bertek Pharmaceuticals) is approved in the US for the treatment of tinea pedis interdigitalis, tinea corporis, tinea cruris, and in August 2001, this drug was approved by the US FDA for the treatment of pityriasis versicolor, a superficial fungal infection caused by Malassezia spp.

Mechanism of Action
Butenafine hydrochloride is a synthetic benzylamine derivative with a mode of action similar to that of the allylamines class of antifungal drugs. Like the allylamines, butenafine inhibits the fungal enzyme squalene epoxidase, thereby blocking the biosynthesis of ergosterol, which is an essential component of fungal cell membranes.

In Vitro Activity
In certain concentrations and against susceptible organisms, such as dermatophytes, butenafine is thought to be fungicidal. Butenafine hydrochloride is active in vitro against many species of fungi, including Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Epidermophyton floccosum, Microsporum canis, and yeasts including C. parapsilosis, C. albicans, and Malassezia spp.

Therapeutic Efficacy
Tinea Pedis 2-4
Butenafine applied once daily for 4 weeks or twice daily for 1 week is effective in the treatment of interdigital tinea pedis. In a multicenter, randomized, double-blind, placebo-controlled study the effectiveness of a once-daily application of butenafine for 4 weeks in the management of interdigital tinea pedis was evaluated. At week 4, the mycologic cure rates (negative light microscopy and culture) in the butenafine and vehicle groups were 91% and 63%, respectively (P<0.01). Four weeks following the discontinuation of therapy, the mycologic cure rates in the two groups were 83% and 38%, respectively (P<0.001).

A second study3 using the same regimen reports that the differences in cure rates between the butenafine and vehicle groups was greatest at 4 weeks post-treatment. This continued increase in the efficacy rate of butenafine until the 4-week follow-up is consistent with data from animal studies that indicate that butenafine persists in the stratum corneum for some time following discontinuation of active therapy.4-6
A multicenter, double-blind, randomized, controlled trial evaluated the efficacy of one-week, twice-daily treatment with butenafine in patients with tinea pedis. Efficacy analysis was performed on 271 patients who were culture positive for tinea pedis (butenafine group: 132, vehicle group: 139). In the butenafine group there was a significantly higher mycologic cure at day 8 compared to the vehicle group (43% vs. 25%, P=0.002).

Similarly, the mycologic cure rates at the 5-week follow-up were 74% vs. 22%, respectively (P<0.0001). Both mycological and clinical cures were found in 23% of patients receiving butenafine, compared to 3% in the vehicle group (P<0.0001). Both mycological and clinical cures were found in 23% of patients receiving butenafine, compared to 3% in the vehicle group (P<0.0001).

Tinea Corporis

A multicenter, randomized, vehicle controlled, double-blind trial evaluated the efficacy of butenafine 1% cream applied once daily for 2 weeks in the treatment of tinea corporis. Efficacy was evaluated in 78 patients (42 butenafine, 36 vehicle). The mycologic cure (negative KOH and culture) was higher in the butenafine group compared to the vehicle group on day 7 (64% vs. 9%, P<0.001) and day 14 (88% compared to 28% of the vehicle group (P<0.0001). At week 4, following completion of therapy, the butenafine group continued to demonstrate a high mycologic cure rate (88%) compared to a decrease in cure rate in the vehicle group to 17% (P<0.0001). At day 14, the overall cure (mycological cure plus 100% clinical remission) in the butenafine group was 31% compared to 3% in the vehicle group (P=0.001). At the week 4 follow-up point, the overall cure in the butenafine and vehicle groups was 67% and 14%, respectively (P<0.0001).

Tinea Cruris

In a multicenter, randomized, vehicle-controlled, double-blind trial, butenafine 1% cream was applied once daily for 2 weeks. The mycologic cure (negative KOH and culture) was higher in the butenafine group compared to placebo as early as day 7. The higher efficacy rate in the allylamine group increased during the 2-week period of active treatment. At the 4-week follow-up point, the mycologic cure rate in the butenafine group was 81% compared to 13% in the vehicle group (P<0.0001). At the end of treatment, the overall cure rate (negative mycology and clinical cure) was 32% in the butenafine group compared to 8% in the vehicle group (P<0.01). At 4 weeks post-treatment, overall cure was achieved in 62% of the butenafine, versus a decrease to 3% for the vehicle group (P<0.0001).

Pityriasis Versicolor

While Malassezia yeasts are normal skin commensals, in some individuals the yeasts transform to a pathogenic, hyphal form, resulting in pityriasis versicolor. In two randomized, controlled trials butenafine and vehicle were applied once daily for two weeks in patients with pityriasis versicolor. In the first study, at 6 weeks post-treatment, 55% of patients receiving butenafine were mycologically cured and 51% were completely cured (i.e., negative mycology and no erythema, scaling or pruritus.). The corresponding numbers for the vehicle group were 36% and 36%, respectively. In the second study, "effective treatment" was defined as negative mycology plus a score of one or less on a 4 point scale (0 to 3) for erythema, pruritus and scaling. At 6 weeks follow-up, 43% of butenafine patients were considered to be effectively treated, versus 26% of the vehicle group.

In addition to the evidence for butenafine’s efficacy in pityriasis versicolor, butenafine has in vivo activity against Malassezia yeasts. Butenafine applied twice-daily for 1 week is effective for treating patients with seborrheic dermatitis, which is also caused by Malassezia spp. This agent is, however, not approved for seborrheic dermatitis.

Tolerability

In controlled clinical trials, 9 of 815 patients (approx. 1%) treated with butenafine cream 1% reported adverse reactions related to the skin. These reactions included burning/stinging of the skin and worsening of the dermatosis. No patients discontinued therapy due to an adverse event. Two of 624 patients receiving the vehicle discontinued therapy because of treatment site related events including severe burning/stinging and itching. In uncontrolled trials, the adverse events most commonly associated with the use of butenafine 1% cream included contact dermatitis, erythema, irritation, and itching, with each occurring in less than 2% of patients.

Dosage and Administration

Butenafine cream 1% is indicated in the US for the topical treatment of interdigital tinea pedis, tinea corporis, and tinea cruris due to T. rubrum, T. tonsurans, T. mentagrophytes, and E. floccosum. In tinea pedis interdigitalis, butenafine cream 1% may be applied twice daily for 7 days or once daily for 4 weeks. In patients with tinea corporis and tinea cruris, it is indicated for once daily application for 2 weeks. For the treatment of pityriasis versicolor, butenafine cream 1% should be applied once daily for 2 weeks.

Continued on page 5
Prevention of Polymorphous Light Eruption and Solar Urticaria

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ABSTRACT

Polymorphous light eruption (PLE) and solar urticaria (SU) are two photodermatoses that are induced by ultraviolet radiation and sometimes by visible light. This article will review the various means of preventing PLE and SU with an emphasis on the role of sunscreens.

Key words: PLE, polymorphic light eruption, solar urticaria

Polymorphous Light Eruption

Polymorphous light eruption is a common photodermatosis with a prevalence as high as 10-20% in Caucasian populations.1,2 Photo-provocation studies have shown that the eruption is triggered by UVA in most patients, although in certain patients UVB alone can trigger the eruption.3-5 In a recent series of 110 patients, PLE could be photoinduced with visible light in 23 patients who were also sensitive to UVB and UVA. The clinical significance of visible light sensitivity in these patients is unknown.6

Because PLE is a self-limited disease that spontaneously resolves when exposure to triggering light is stopped, the focus is centered on prevention. Sun protection and sun avoidance are central for PLE prevention. The level of photoprotection necessary to avoid the development of the eruption varies from patient to patient. For most patients with mild disease, avoidance of intense sun exposure, especially in the winter or early spring is sufficient to prevent the eruption. However, for some patients, seeking the shade and avoidance of intense sun exposure is not enough. Sunscreens have been recommended for these patients even though efficacy of earlier sunscreens has been low, probably because of their limited UVA protection.7

Sunscreen for the Treatment of PLE

We recently compared the efficacy of two high SPF sunscreens for the prevention of indoor PLE generated by metal halide lamps.8 The two sunscreens compared were Coppertone® 45 which contains only oxybenzone for UVA protection and Anthelios® L, which contains Mexoryl SX, Parosol® 1789 and titanium dioxide (TiO2) for UVA protection. UVA protection by oxybenzone is limited to short-wave UVA. Anthelios® L prevented PLE in all patients, whereas Coppertone® 45 was able to prevent PLE in only 3 patients out of the 23 who completed the study.

To further explore UVA protection afforded by sunscreens we compared the ability of 6 sunscreens with SPF of 21 or more to prevent pigmentation induced 2 hours after artificial UV exposure.9 The sunscreens compared were: Anthelios® L 60, Bain de Soleil® 25, Coppertone® 45, Hawaiian Tropic® 50, Presun® 21 and Presun® 30. In order of decreasing efficacy the best sunscreens for UVA protection were Anthelios® L, Presun® 30, PreSun® 21, Bain de Soleil® 25, Coppertone® 45 and Hawaiian Tropic® 50. In this study the two sunscreens that afforded the highest UVA protection contained Parsol® 1789, which has a maximal absorption at 358nm. Anthelios® L also contained Mexoryl SX for UVA protection, which has a maximal absorption at 345nm. The two sunscreens containing physical agents only (i.e., PreSun® 21 and Bain de Soleil® 25) were not as efficient for UVA protection, which could be related to the fact that the spectral protection of micronized titanium dioxide (TiO2) decreases with increasing UVA wavelength.10 This study confirmed that SPF, a measure of UVB protection, is not indicative of UVA protection provided by sunscreens. It also illustrates how difficult it is to select a sunscreen with broadspectrum and high UVA protection, since SPF is the only indicator of UV protection on sunscreen labels in North America.

Photostability is another important parameter to consider when selecting a sunscreen that provides good UVA protection. Parsol® 1789 is known to be photounstable in certain preparations.11 Unfortunately, it is not possible to know if a sunscreen is photostable only by looking at the label, because there is no information on this subject on labels in North America.

Prophylactic Treatments

Prophylactic treatments with UVA, UVB or PUVA therapy can prevent PLE in certain patients.12,13 Although PUVA therapy is effective, its use has to be weighed against the risks of squamous cell carcinoma and melanoma.14 A topical formulation containing the antioxidants tocopheryl acetate, ferulic acid and α-glycosylrutin was reported to prevent the development and reduce the severity of indoor PLE in certain patients,15 suggesting that the role of antioxidants in sunscreen formulations deserves further study.
Solar Urticaria

Solar urticaria (SU) is photodermatosis characterized by urticarial papules and plaques appearing typically after 5-10 minutes of sun exposure, with spontaneous disappearance after a few hours of sun avoidance. The spectrum of solar urticaria induction varies according to patients and can include UVA, UVB as well as visible light. Visible light alone can induce SU, and a recent Japanese series reported that as many as 60% of patients were sensitive to visible light. Visible light alone can induce SU,

SU and Sunscreens

SU is a problem as far as sunscreens are concerned, because the protection afforded by sunscreens in the visible range is not very good. The absorption spectrum of chemical sunscreen agents is limited to the UV range of the solar spectrum. Although opaque non-micronized physical agents may reduce visible light transmission, patients are reluctant to use opaque sunscreens. An in vitro spectroscopic study suggested that sunscreens with iron oxide offer a better protection against visible light than titanium dioxide or zinc oxide. RV Paige® is a sunscreen containing 1.7% of iron oxide. The disadvantage of iron oxide is that it gives a red-brown colour to sunscreens. Dihydroxyacetone can also protect against the lower portion of the visible spectrum. Many sunless tanning lotions contain dihydroxyacetone. With the current developments in the field of photodynamic therapy, which consists of administering drugs that make patients sensitive to visible light, there is renewed interest in the development of sunscreens that offer better protection in the visible range.

Other Treatments for SU

Antihistamines can be valuable for SU, but their use is often disappointing for patients with severe disease. Other treatments that have been used with limited success include UVB, narrow band UVB and PUVA therapy. Plasmapheresis has been used in selected cases with success. This approach is useful for patients, in which it is possible to induce urticarial plaques following in vitro irradiation of their own serum, suggesting that the improvement could be related to removal of the antigen by plasmapheresis. Interestingly, this modality has been shown to induce remissions of more than a year in certain patients.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Sunscreen</th>
<th>SPF</th>
<th>Active Ingredient</th>
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<tbody>
<tr>
<td>1</td>
<td>Anthelios L®</td>
<td>60</td>
<td>• Mexoryl SX</td>
</tr>
<tr>
<td></td>
<td>(LaRoche-Posay)</td>
<td></td>
<td>• Parsol® 1789</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• TiO₂</td>
</tr>
<tr>
<td>2</td>
<td>PreSun®</td>
<td>30</td>
<td>• Parsol® 1789</td>
</tr>
<tr>
<td>3</td>
<td>PreSun®</td>
<td>21</td>
<td>• TiO₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ZnO₂</td>
</tr>
<tr>
<td>4</td>
<td>Bain de Soleil®</td>
<td>25</td>
<td>• TiO₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ZnO₂</td>
</tr>
<tr>
<td>5</td>
<td>Coppertone®</td>
<td>45</td>
<td>• Ethylhexyl P-Methoxycinnamate</td>
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<td></td>
<td></td>
<td></td>
<td>• Oxybenzone</td>
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<td></td>
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<td>• 2-Ethylhexyl Salicylate</td>
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<td></td>
<td></td>
<td></td>
<td>• Homosalate</td>
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<tr>
<td>6</td>
<td>Hawaiian Tropic®</td>
<td>50</td>
<td>• Octocrylene</td>
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<td></td>
<td></td>
<td></td>
<td>• Octyl Methoxycinnamate</td>
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<td>• Octyl Salicylate</td>
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<tr>
<td></td>
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<td>• TiO₂</td>
</tr>
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Table 1: Six sunscreens with SPF ratings >21 in order of decreasing efficacy tested to prevent pigmentation induced 2 hours after artificial UV exposure.

Conclusion

In conclusion, PLE and solar urticaria can be prevented in most patients by decreasing their amount of sun exposure and by using an adequate sunscreen. As UVA is mainly involved in the induction of both diseases, the sunscreen used should contain broad as well as high UVA protection.

References


### Update on Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsoriatic Agent</strong></td>
<td>Tazarotene</td>
<td>TPP - Canada approved two additional indications for this antipsoriatic agent, one in May 2002, and the second in June 2002. It is now also indicated for the topical treatment of acne vulgaris, and photodamaged skin.</td>
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<tr>
<td></td>
<td>Clorizine® 0.1% Cream Allergan</td>
<td></td>
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<tr>
<td><strong>Anti-acne Agent</strong></td>
<td>Isotretinoin</td>
<td>The US FDA approved updated labeling for this anti-acne agent in May 2002. This labeling warns of the risk of musculoskeletal adverse effects. The new warning states that the link to Accutane® has not been established, but that care should be taken and the drug should be used no longer than the recommended duration of therapy.</td>
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<tr>
<td></td>
<td>Accutane®</td>
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<td>Hoffman-La Roche</td>
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<tr>
<td><strong>Antihistamine</strong></td>
<td>Desloratidine</td>
<td>The US FDA approved this antihistamine in June 2002, for the treatment of allergy symptoms caused by perennial indoor and seasonal outdoor allergens and chronic idiopathic urticaria in adults and children 12 years of age and older. This product is a rapidly disintegrating formulation and its launch is planned pending US FDA approval of a quality control test revision.</td>
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<td></td>
<td>Clarinex® 5mg Reditabs Schering-Plough</td>
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<tr>
<td><strong>Antiviral Agent</strong></td>
<td>Imiquimod</td>
<td>The US FDA approved a new indication and dosage in May 2002, for the treatment of genital and perianal warts and condylomata acuminata. The new dosage approved: apply a thin layer to warts at h.s. 3 times weekly for a maximum of 16 weeks.</td>
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<td></td>
<td>Aldara® 3M Pharmaceuticals</td>
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### Drug News

**Antipsoriatic Agent**

Soriatane® (acitretin, Hoffman-La Roche) won two Gold Triangle awards from the American Academy of Dermatology. The first award was in the Industry Communications Campaign category for its Psoria-Sense Patient Education Program, which is a web, e-mail and direct mail-based education program for psoriasis patients. The second award was in the Print Advertising category for a professional sales brochure and ad campaign about the importance and effectiveness of maintenance therapy for psoriasis using this product. The Gold Triangle awards honor excellence in furthering the understanding of dermatologic issues.

**Malpractice Concerns in US**

In July 2002, the President of the AADA, Fred F. Castrow II, made a presentation before the US House of Representatives, expressing the views of the AADA membership regarding health care litigation reform. He stated that they are very concerned about the current medical malpractice insurance marketplace. Because many of the major insurance companies have stopped carrying this type of insurance, liability premiums are rising, and physicians across the US have reported that they are unable to obtain medical liability insurance. In 2001, eight states saw two or more liability insurers raise their rates by at least 30%. In some areas, only one insurer remains, forcing physicians to face an all or nothing proposition. Dr. Castrow urged the House subcommittee to act favorably on H.R. 4600, the "Help Efficient, Accessible, Low Cost, Timely Health Care 'HEALTH' Act of 2002". This legislation contains much needed medical liability reforms, while continuing to ensure that patients who have been injured through negligence are fairly compensated. Members of the AADA believe that H.R. 4600 will ensure the stability and viability of the health care system in the US.