Naftifine Treatment of Resistant Dermatophytosis

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Abstract: Despite an array of topical and systemic antifungal agents, cases of resistant dermatophytosis still exist. Use of naftifine, the first commercially available allylamine derivative, proved successful in the management of four such cases.

Dermatophytoses can provide a therapeutic dilemma, especially when they are persistent despite multiple modes of treatment. The most common forms of therapy include administration of topical and systemic imidazoles, and systemic administration of various forms of griseofulvin. A new antimycotic agent, naftifine ([E]-N-cinnamyl-N-methyl-1-napthalenemethylamine hydrochloride), initially synthesized by the Wonder Laboratories in Berne,[1] was discovered to have antifungal activity by the Sandoz Research Institute in Vienna.[2,3] Both *in vitro* laboratory and *in vivo* clinical trials have shown naftifine to be highly effective against a variety of dermatophytes and moderately effective against molds and yeasts.[4–10]

We present four patients with recalcitrant (treatment-resistant) dermatomycoses who responded to naftifine therapy within 4 weeks. All patients have remained relatively free of their heretofore vexing fungal infections.

Case Reports

Case 1

- A 54-year-old hispanic man with a 34-year history of widespread tinea corporis presented with erythematous, irregular, scaly patches involving almost his entire chest, back, abdomen, buttocks, feet, and scattered areas on the thighs and face (Fig. 1). The lesions showed innumerable hyphae on potassium hydroxide (KOH) preparation, and *Trichophyton rubrum* grew on culture. An extensive immunologic work-up gave normal results. The patient failed twice daily topical applications of Whitfield's ointment, Castellani's paint, clotrimazole, econazole, spectazole, ciclopirox olamine, miconazole, and 2% sulfur. He also failed systemic administration of griseofulvin (1 g/day), ketaconazole (discontinued due to development of liver function abnormalities), cimetidine (attempt to increase cell-mediated immunity), and isotretinoin (attempt to desquamate the skin). He was started on naftifine 1% cream twice a day and had a striking response after 1 month. After 2 months of continued therapy, his face was totally clear and his trunk was approximately 80% clear. His lesions have remained stable, and he is markedly improved from a symptomatic standpoint.

Case 2

- A 30-year-old white man with the diagnosis of AIDS presented with a 1-month history of a foot dermatitis. On examination, the dorsa of the left foot had several annular, erythematous, scaly plaques. Potassium hydroxide preparation revealed innumerable hyphae, but a culture was not done. The patient failed sequential 6-week trials of topical clotrimazole and ciclopirox olamine, and the KOH preparation remained strongly positive. Therapy with naftifine 1% cream was then initiated, and most of the scaling and erythema had resolved in 2 weeks. After 4 weeks of treatment, the foot was clear. The patient was seen 7½ months after discontinuing the naftifine, and there was no clinical evidence of dermatophytosis.

Case 3

- A 23-year-old white man, otherwise in excellent health, presented with a 5-year history of an eruption involving the left thigh, left flank, both buttocks, and the left side of the face. Physical examination showed erythematous, annular, scaly patches in these areas. A KOH preparation was highly positive, and fungal culture yielded *Trichophyton rubrum*. The patient did not respond to diligent, twice-daily application of clotrimazole and clotrimazole–betamethasone creams. Two weeks after initiation of treatment with naftifine 1% cream, all areas were clinically and mycologically clear. During a tele-

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phone follow-up 6 months after discontinuing therapy, the patient denied any recurrence.

Case 4

- A 63-year-old black man presented with generalized tinea corporis of approximately 30 years' duration. He had multiple medical problems, including adult-onset diabetes mellitus, hypertension, recurrent urinary tract infections, stable angina due to coronary artery disease, and sleep apnea. Physical examination revealed widespread annular, erythematous, scaly patches involving all four extremities, both anterior and posterior aspects of the trunk, and the buttocks. A KOH preparation was strongly positive, and fungal culture disclosed *Trichophyton rubrum* to be the causative organism. The patient had previously failed to improve, despite prolonged topical applications of clotrimazole and econazole and despite oral griseofulvin (1 g/day) therapy. Following 2 weeks of twice-daily applications of naftifine 1% cream, many areas had totally resolved (Fig. 2); after 1 month of treatment, 90% of all involved skin was clinically and mycologically normal.

Discussion

Naftifine, an allylamine derivative, has been found to have a different mechanism of action than that of the imidazoles. By selectively inhibiting squalene epoxidase, this agent causes an accumulation of squalene to develop within the fungus, as well as causing a decrease in the production of ergosterol.[11,12] The latter is necessary for normal fungal membrane synthesis. In *Candida albicans*, at levels inhibiting ergosterol biosynthesis, naftifine produces a decrease in the ratio of unsaturated to saturated fatty acids, in turn leading to a decrease in membrane integrity.[13] Such effects are believed responsible for this agent's antimycotic action. Naftifine also may inhibit RNA polymerase and chitin synthetase in some fungi as additional antimycotic mechanisms.[14] By contrast, imidazoles exert their antifungal action by preventing 14-demethylation of lanosterol,[15] thereby also inhibiting ergosterol production, but at a later point in the sterol synthetic pathway. Therefore, there is no increase in intracellular squalene content associated with imidazole therapy. This is believed to be the reason why the imidazoles are fungistatic at typical therapeutic concentrations,[16] in comparison to allylamines, which are fungicidal.[2,11,17]

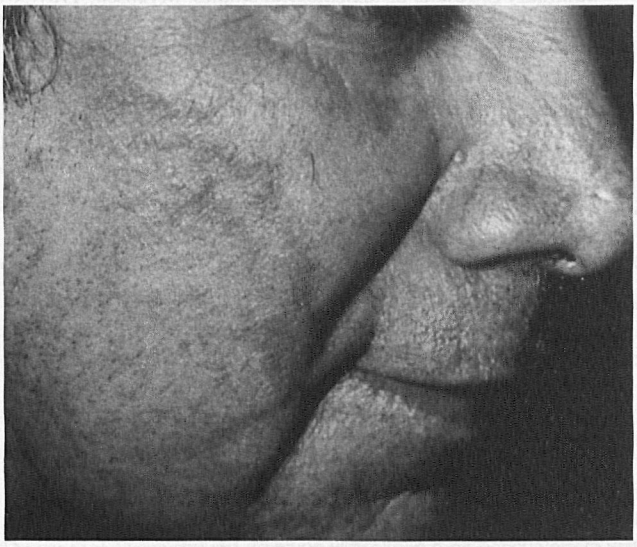

Figure 1. Annular lesion of tinea on the cheek (case 1).

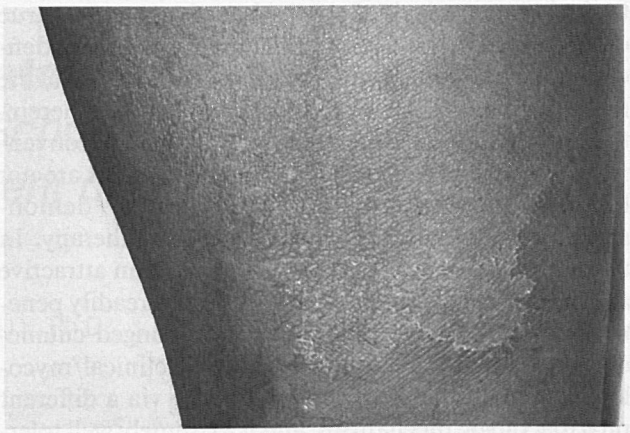

Figure 2. One of immunerable lesions of tinea corporis, pretreatment (case 4).

Response to topical antifungal medication depends not only on the medication's direct antimycotic activity, but also on the ability of the agent to penetrate the epidermis. In a variety of preparations, naftifine has been shown to easily penetrate the stratum corneum, to inhibit fungal growth therein, and to remain present in the upper horny layers of the skin for several days after a single application.[10,18] Such persistence allows for once-daily use, the latter proving to be as effective as twice-daily application.[18,19] Moreover, topical naftifine has also been demonstrated to be generally free of the potential for allergic or irritant dermatitis, photosensitization, and phototoxicity,[20,21] although rare cases of true contact dermatitis have been reported.[22]

It is also worth noting that, in preclinical *in vitro* and *in vivo* studies of antifungal activity, naftifine proved *superior* to both clotrimazole and econazole.[23] Cumulative experience in published clinical studies also suggests that naftifine is actually superior to imidazole agents, as indicated by a higher mycologic cure rate and more marked and rapid improvement in clinical signs and symptoms of dermatophytosis.[5–8]

A patient's unresponsiveness to any given antifungal treatment may be related to a lack of penetration of

topical agents, a lack of absorption of oral agents, true drug resistance of the organism, host immunodeficiency, lack of compliance, or some combination of the foregoing factors. In the four patients reported herein, the exact etiologies of their failure to respond to conventional topical and/or oral antifungal treatment are not known. Nonetheless, each patient clearly demonstrated clinical failure following standard therapy. In this situation, naftifine theoretically offers an attractive alternative mode of treatment. This agent readily penetrates the epidermis; demonstrates prolonged cutaneous persistence; yields reliable and rapid clinical/mycologic cures; provides fungicidal activity via a different pharmacologic mechanism; and is extremely well tolerated. Indeed, in our patients, naftifine therapy proved to be of more than theoretical advantage, resulting in dramatic clinical responses in patients with long-standing, recalcitrant dermatophytoses.

Drug Name

naftifine 1% cream: Naftin cream

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Skin Remedies from the Middle English Period

For instance, cress (nasturtium) was much prized—"In case a man's hair fall out, take juice of the wort which one names nasturtium or cress—put in nose and the hair shall grow." For warts (boils) wort and yeast were pounded together and then applied. For a sore head, the scurf and the itch, the seed of wort and goose grease were pounded together. This "draws from off the head the whiteness of the scurf." For dimness of the eyes the juice of wild lettuce was mixed with honey and with old wine and this was said to be a wonderful cure. A similar mixture was taken for liver troubles.

Animal products were often advised—bull's blood, for instance, could be applied for facial markings and different parts of the goat were used for leprosy, cancer, dropsy, headache and insomnia. To cure leprosy, goats' urine was mixed with honey and salt and rubbed on head and body. For insomnia one slept with a goat's horn under the head and for headache freshly made cheese from goat's milk could be bound to the head.—*Hart F. Anglo-saxon cures Br J Clin Pract 1988;42:250.*