CLINICAL TRIAL

COMPARATIVE EFFICACY OF NAFTIFINE, OXICONAZOLE, AND TERBINAFINE IN SHORT-TERM TREATMENT OF TINEA PEDIS

GLYNIS ABLON, M.D., TED ROSEN, M.D., AND JEANNE SPEDALE, M.D.

The subjects, men ranging in age from 25 to 80 years, were recruited from an ambulatory-care dermatology clinic. The diagnosis of tinea pedis was verified by both a positive KOH preparation and a positive culture for dermatophytes on Sabouraud's agar. Assessment of disease severity was made using a four-point scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Specific signs and symptoms assessed included: fissuring, erythema, maceration, vesicle formation, scaling, exudation, pruritus, and burning/stinging. The overall severity score was determined by the sum of the scores for all of these parameters. A minimum pretreatment cumulative severity score of 3 was required to enroll in the study.

The purpose of the present study was to determine the comparative efficacy for treatment of tinea pedis of two commercially available allylamines (naftifine and terbinafine) and one imidazole (oxiconazole) in a short-term, once daily regimen. It was also our purpose to ascertain the relative efficacy for a longer period of time than typically reported in such studies, namely at 2 months (rather than 2 weeks) following cessation of therapy.

By computer-generated random assignment, study subjects were asked to apply either naftifine gel, terbinafine cream, or oxiconazole lotion to all affected areas, once daily for 2 weeks. Although the agent utilized was known to the dispensing investigator, the evaluating investigator was blinded. The mean initial cumulative severity scores for the three groups were: naftifine gel 6.74, terbinafine cream 6.36, and oxiconazole lotion 6.42. There was no statistical difference between these groups. There was one evaluable case in each treatment group of acute vesiculobullous tinea pedis; the remainder of all evaluable cases had both interdigital and plantar scaling present. Patients with clinically obvious onychomycosis were excluded from participation in the study.

Mycologic examination, consisting of KOH preparation and culture, and the global severity rating (using the same parameters and same four-point system) were repeated at the conclusion of the treatment period and at 1 month and 2 months following cessation of therapy. Mycologic "cure" was defined as negative KOH preparation and negative culture. Clinical "cure" was defined as a total severity score equal to 1 or 0 during any study visit.

Statistical comparisons between treatment groups with reference to mycologic and clinical status were made using the two-tailed Fisher's Exact Test. The chi-square test was used to determine the statistical significance of persistence of clinical and mycologic cure within each medication cohort.

From the Department of Dermatology, Baylor College of Medicine, and Veterans Affairs Medical Center, Houston, Texas.

Address for correspondence: Ted Rosen, M.D., Dermatology Department, 1 Baylor Plaza, Houston, TX 77030.

RESULTS

Efficacy analyses were based upon data from 90 evaluable of the 99 enrolled subjects. Of the 99 enrolled patients, none were lost due to adverse reactions. In the naftifine group, two were dropped because of negative cultures despite a positive KOH preparation, and two did not keep follow-up appointments. In the oxiconazole group, three were dropped due to negative initial cultures and two decided to discontinue participation due to lack of efficacy after the initial treatment period. In the terbinafine group, two subjects failed to report for the final evaluation visit, although their results were still used at weeks 2 and 6.

All positive cultures were identified by species. Infections were attributed to *Trichophyton rubrum* in 57.8% (52/90), *Trichophyton mentagrophytes* in 37.8% (34/90), *Epidermophyton floccosum* in 3.3% (3/90), and *Microsporum canis* in 1.1% (1/90). The two common pathogens were essentially divided equally among treatment groups.

The raw data indicate that terbinafine, naftifine, and oxiconazole provided mycologic cure rates of 33.3%, 34.5%, and 21.4%, respectively, at the conclusion of the treatment phase of the study (Table 1). There was no statistically significant difference between the agents at this point in the study (Table 2); however, one month later, mycologic cure rates for terbinafine and naftifine had risen to 84.8% and 69.0%, respectively, whereas

Table 1. Raw Cure Rates (in Percent)

Treatment Group	*Week 2*	*Week 6*	*Week 10*
Terbinafine			
Clinical cure	42.4	84.8	83.8
Mycologic cure	33.3	84.8	80.6
Naftifine			
Clinical cure	27.6	69.0	75.0
Mycologic cure	34.5	69.0	75.0
Oxiconazole			
Clinical cure	17.9	32.1	30.8
Mycologic cure	21.4	32.1	26.9

Table 2. Statistical Analysis of Data

Comparison of Treatment Groups	*Weeks 2–6*	*Weeks 6–10*	*Weeks 2–10*
Terbinafine vs naftifine			
Clinical cure	NS (0.290)	NS (0.373)	NS (0.521)
Mycologic cure	NS (1.000)	NS (0.223)	NS (0.755)
Terbinafine vs. oxiconazole			
Clinical cure	NS (0.0534)	0.000186*	0.0000984*
Mycologic cure	NS (0.394)	0.0000507*	0.00000585*
Naftifine vs. oxiconazole			
Clinical cure	NS (0.530)	0.00808*	0.00234*
Mycologic cure	NS (0.379)	0.00808*	0.000890*

NS: Not significant; *Statistically significant ($P < 0.05$).

the oxiconazole cure rate remained low (32.1%). Two months after cessation of therapy, terbinafine and naftifine provided mycologic cure rates of 80.6% and 75%, respectively, while the oxiconazole cure rate again remained inferior (26.9%). Although both allylamines proved significantly better than oxiconazole ($P = 0.00132$ terbinafine versus oxiconazole; 0.00257 naftifine versus oxiconazole), there was no statistically significant difference between the two allylamines at week 10 ($P = 0.755$ terbinafine versus naftifine).

The chi-square test indicated that both terbinafine and naftifine provided statistically significant increasing mycologic cure rates for week 2 versus week 10, whereas oxiconazole did not do so.

The clinical cure rates among the three agents did not differ significantly at the conclusion of treatment: terbinafine 42.4%, naftifine 27.6%, and oxiconazole 17.9% (see Tables 1, 2 for details). Clinical cure rates of the three study drugs did differ with statistical significance by week 6: terbinafine 81.8%, naftifine 69%, and oxiconazole 32.1%. Both terbinafine and naftifine were superior to oxiconazole ($P = 0.000186$ and 0.00808, respectively). At 10 weeks, the clinical cure rates for terbinafine (83.8%) and naftifine (75%) remained superior to the 30.8% clinical cure rate for oxiconazole ($P = 0.00098$ and 0.00234, respectively). No superiority of one allylamine over another could be demonstrated at 2, 6, or 10 weeks ($P = 0.290$, 0.373, and 0.521, respectively).

The clinical cure rates with allylamine drugs improved when comparing initial against subsequent results; but oxiconazole did not provide similarly improving results with time that were of statistical significance.

Table 3. Analysis of Each Agent's Performance over Study Time Periods

Treatment Groups	*Weeks 2–6*	*Weeks 6–10*	*Weeks 2–10*
Terbinafine			
Clinical cure	0.000870*	NS (1.00)	0.000510*
Mycologic cure	0.000240*	NS (1.00)	0.00132*
Naftifine			
Clinical cure	0.00328*	NS (0.480)	0.00195*
Mycologic cure	0.00937*	NS (0.683)	0.00257
Oxiconazole			
Clinical cure	NS (0.221)	NS (1.00)	NS (0.450)
Mycologic cure	NS (0.371)	NS (0.480)	NS (1.00)

NS: Not significant; *Statistically significant (P values < 0.05).

DISCUSSION

Despite many claims regarding the inherent superiority of various topical antifungals, there remains a paucity of directly comparative, *in vivo* investigation. Moreover, many of the studies published to date have such a brief posttherapy follow-up, that their relevance to the treatment of chronic dermatophytoses (such as tinea pedis) is questionable.

This study was designed to address several questions simultaneously. First, can any of the three agents tested provide acceptable clinical and mycologic cure rates following a short-term treatment course? Are the cure rates maintained over at least 2 months? Are the allylamines superior to a recently introduced imidazole? Finally, is one allylamine superior to the other?

Short-term therapeutic regimens seem logical in view of the high potency and fungicidal properties of allyalamines,[1–4] as well as their capacity to remain active even after treatment is discontinued due to keratin binding.[5,6] Short-term regimens are certainly preferable, both to enhance compliance as well as to reduce cost. Although our results indicate relatively low clinical and mycologic cure rates immediately following a two-week, once-daily treatment regimen, at both 4 and 8 weeks after cessation of therapy, the allylamines ultimately provided very acceptable rates of success. In contrast, the fungistatic imidazole, oxiconazole, provided poor clinical and mycologic cure rates throughout the study. It is likely that this agent requires initial treatment periods longer than previously published to achieve comparable long-term success.[7,8]

Although data support the use of allylamines in tinea pedis, the available studies generally compare these agents to either a placebo or an older imidazole.[9–13] Thus, this study provides additional information regarding the efficacy of allylamine agents when compared to a newer imidazole and to each other. Although it appears, that the two commercially available allylamines perform equally well in the treatment of tinea pedis; considerations such as vehicle and cost may be the deciding factors in choosing between them. In previous studies, short-term treatment regimens using allylamines were found to be beneficial in interdigital tinea pedis.[14,15] Our data suggest that with slightly longer treatment (2 weeks instead of 1), even chronic tinea pedis may well be resolved in a high percentage of cases.

DRUG NAMES

naftifine: Naftin
oxiconazole nitrate: Oxistat
terbinafine: Lamisil

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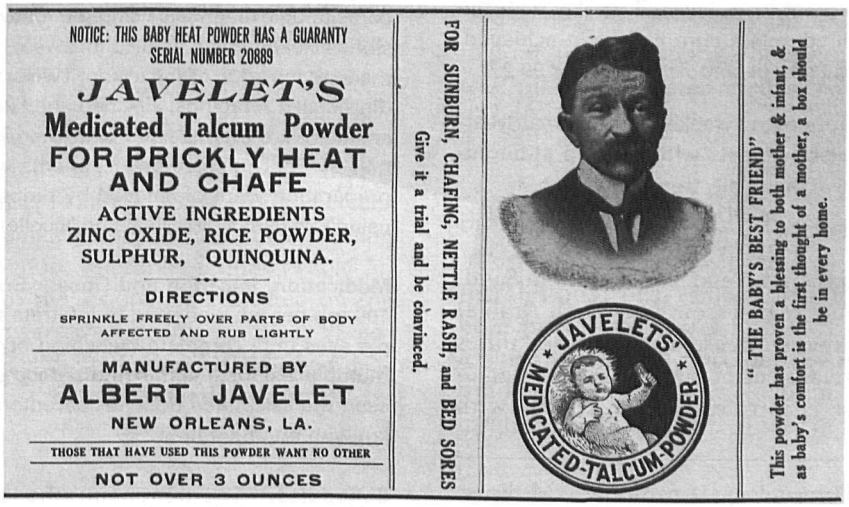

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