Topical Miconazole Nitrate Ointment in the Treatment of Diaper Dermatitis Complicated by Candidiasis

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Diaper dermatitis (DD) complicated by candidiasis is a common problem in diaper-wearing infants and children. We report a double-blind, vehicle-controlled, parallel-group study evaluating the efficacy and safety of a low concentration of miconazole nitrate in a zinc oxide/petrolatum ointment for the treatment of DD complicated by candidiasis. Patients (N=330) who had DD with a severity score of 3 or higher were enrolled. Those patients with a baseline potassium hydroxide (KOH) preparation and a baseline culture specimen that both tested positive for Candida *were retained for efficacy analysis (n=236). Miconazole nitrate 0.25% ointment or a zinc oxide/petrolatum vehicle control were applied to all clinically affected areas of patients with DD for 7 days at each diaper change and after bathing. A follow-up test-of-cure visit was conducted at day 14. Among the patients completing the study, the overall rate of cure (clinical cure plus microbiologic cure) was 23% for the miconazole nitrate group and 10% for the vehicle control group (*P=.005*); the rate of clinical cure (complete rash clearance, DD severity score=0 at day 14) was 38% for the miconazole nitrate group and 11% for the vehicle control group (*P<.001*); and the rate of microbiologic cure (no culture growth of* Candida*) was 50% for the miconazole nitrate group and 23% for the vehicle control group. The vehicle control resulted in mild improvement at day 3 but little or no subsequent improvement. The discontinuation rate due to clinical failure was substantially lower for the miconazole nitrate group (4%) than the vehicle control group (47%). The mean DD severity index score for the miconazole nitrate group was significantly lower from day 3 through day 14 compared with that of the vehicle control group (*P<.001*). Adverse events were assessed as either unlikely to be related to study medication or unrelated to study medication. By including only those patients with microbiologically confirmed* Candida *infection, the study population may not be fully indicative of patients treated for DD in routine clinical practice. Our data show that miconazole nitrate 0.25% ointment was well tolerated and significantly more effective than the zinc oxide/petrolatum vehicle control for treatment of DD complicated by candidiasis.*

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Diaper dermatitis (DD) is the most common dermatologic disorder of infancy,[1] with the highest prevalence occurring between the ages of 9 and 12 months.[2] Although an association between DD and *Candida* was first reported more

than 35 years ago,[3] the condition remains a common problem among diapered infants and young children.[1,2] The pathophysiology of this condition has been largely clarified,[4] but questions remain. For example, what conditions must be present before *Candida* can infect the skin of the diaper area? More specifically, is the mere presence of *Candida* sufficient, or must the epidermal surface be compromised?

Topical antifungal therapy is warranted when *Candida* infection is suspected or confirmed. Clinicians treat DD complicated by candidiasis with a number of topical antifungal prescription and over-the-counter products, including miconazole 2%. Some clinicians also treat patients with an antifungal medication that contains a high-potency topical corticosteroid such as clotrimazole and betamethasone dipropionate; however, these combination topical formulations are inappropriate for use in intertriginous areas,[5] and the US Food and Drug Administration (FDA)–approved labeling carries specific bolded precautions against their use in patients younger than 17 years or in pediatric patients with DD.[6]

No prescription product for the treatment of DD complicated by candidiasis currently is approved by the FDA. Not all infants respond readily to topical antifungal treatment of DD complicated by candidiasis, and the condition may recur. The literature provides little guidance regarding optimal therapy, and evidence supporting the efficacy of most therapeutic approaches mostly is anecdotal. With the exception of one well-controlled Australian trial,[7] published studies of DD in infants and young children are small and unblinded[8] or do not consider the role of *Candida*.[9] Similarly, there are scant data regarding the tolerability of topical antifungal agents applied to the diaper area of infants. The incidence of associated discomfort, local irritant, or allergic contact reactions in this setting is unknown.

We conducted this study to determine whether a low, 0.25% concentration of miconazole nitrate in a zinc oxide/petrolatum vehicle is an effective and well-tolerated treatment for DD complicated by candidiasis. The study was designed to redress the deficiencies in previous studies of DD complicated by candidiasis, and we believe it to be the largest controlled study of DD complicated by candidiasis performed to date.

Materials and Methods

Participants—This double-blind, vehicle-controlled, randomized, parallel-group, multicenter study was conducted between April 2003 and June 2004 at 20 academic, clinical, or research sites in the United States (n=16) and Latin America (n=4). The study was approved by the FDA as well as by appropriate institutional review boards. An authorized caretaker (parent or legal guardian) signed an informed consent form before the performance of any study-related activity. Male and female neonates, infants, and children younger than 4 years who wore commercially available diapers day and night, had clinical evidence of DD at baseline, and had a DD severity index score of 3 or higher were eligible for inclusion. A DD severity index score was calculated as the sum of severity grades for erythema (0=none to trace, 1=mild [pink], 2=moderate [red], 3=severe [beefy red]); papules or pustules (0=none to trace, 1=few [1–10], 2=multiple [11–20], 3=many [21–40], 4=abundant [>40]); and erosions (0=absent, 1=present). A severity grade of at least 2 for erythema was required for inclusion. A total score of 3 to 4 was considered "moderate" and a score of 5 to 8 was considered "severe" (the maximum possible score was 8). Clinical evaluations were performed on days 0 (baseline visit), 3, 5 (optional), and 7 (end-of-treatment visit), with follow-up clinical evaluation on day 14 (test-of-cure visit). Whenever possible, the same investigator performed all clinical assessments for a given patient throughout the study. Rate of relapse, if any, was assessed by telephone follow-up on day 28.

At the baseline visit, a potassium hydroxide (KOH) preparation was immediately examined microscopically for pseudohyphae and/or budding yeasts, and a positive test result was required for retention in the study. Also required was a positive culture result for *Candida* that was obtained at baseline from specimens taken from the involved area of DD. Speciation of the culture specimens was determined at the Fungus Testing Laboratory, University of Texas Health Science Center, San Antonio. Specimens were taken from the most clinically affected areas of DD, either from the periphery of the rash (raised border, flaking) or from a pustule after deroofing to include the roof of the pustule and its contents. A follow-up KOH preparation and a culture specimen for *Candida* were obtained from the involved area of DD on days 7 and 14, and at the time of early discontinuation due to clinical failure. Patients admitted to the study whose baseline culture specimen results were found to be negative were discontinued and excluded from the efficacy evaluation but were included in the safety evaluation.

Exclusion criteria were known sensitivity to skin care toiletry products, diapers, or any of the formulation components; the presence of any dermatosis other than DD; chronic illnesses that required

systemic medication (other than antibiotics) that could confound the evaluation of drug efficacy and tolerability; or treatment with a prescription product for DD or any other dermatosis within 7 days of enrollment.

Interventions—Patients who met all inclusion criteria were randomized at each site to receive miconazole nitrate 0.25% ointment or zinc oxide/petrolatum vehicle control, which were provided in identical-appearing 30-g tubes by a third-party dispenser who neither performed the clinical evaluations nor obtained or examined the mycologic samples.

Each patient's caretaker received 2 tubes of their assigned study drug and was instructed to apply the drug with the fingertips to clinically affected areas of the patient at each diaper change and after each bath for a total of 7 days, even if all signs of DD were no longer visible. Use of any other topical products was not permitted during the study. Caretakers kept a daily diary during the 7-day treatment-evaluation period that indicated the number of times the study drug was applied, the number of diaper changes, and any change in diaper brand.

Outcomes—The primary outcome measure was the therapeutic response, or "overall cure," which was the combined result of the clinical and microbiologic responses. Overall cure required that patients be assessed as both clinically cured (defined as a DD severity index score of 0) and microbiologically eradicated (defined as no growth of *Candida*) on day 14. Other combinations of results (ie, DD severity index score >0 and/or growth of *Candida*) were considered "treatment failure." Any patient for whom the day-14 culture result was unavailable or unreliable and any patient who discontinued or was lost to follow-up also was considered a treatment failure. The primary evaluation of therapeutic efficacy was based on the proportion of patients with a therapeutic response of overall cure out of all patients evaluated for therapeutic response. Assessments of clinical cure and microbiologic eradication on day 14 were considered secondary outcome measures.

Evaluation of tolerability included the incidence and severity of adverse events. At the discretion of the investigator, patients could be withdrawn from the study at any time if clinically relevant drug-related emergent signs or symptoms arose or if continued treatment with the study drug possibly would not be in the best interest of the patient, such as worsening DD or insufficient improvement.

Statistical Methods—Statistical analyses were performed on 3 patient groups: (1) the modified intent-to-treat (MITT) population, the primary population for efficacy analysis, defined as all patients with confirmed *Candida* who were dispensed study medication; (2) the per-protocol (PP) population, the secondary population for efficacy analysis, defined as all patients in the MITT population who completed the study with no noteworthy protocol violations, no early discontinuations due to treatment failure, or no treatment-related adverse events; and (3) the safety population, defined as all patients who were dispensed study medication and who subsequently provided post-baseline information.

The statistical significance of any treatment group difference was tested using a 2-sided Cochran-Mantel-Haenszel test. The comparability of the groups was analyzed using an analysis of variance model at each of the visits. The change from baseline to day 3 and the difference between treatments on days 3, 5, 7, and 14 also were determined with a comparison *P* value calculated using an analysis of variance model. The Cochran-Mantel-Haenszel test was used to assess the day-14 clinical cure rates. The 2-sided Fisher exact test was used to compare the proportion of patients in each treatment group with any adverse event to assess tolerability.

Results

Of the 330 patients who met the entry criteria and were enrolled in the study, 236 were included in the MITT population (112 in the miconazole nitrate 0.25% ointment group and 124 in the zinc oxide/petrolatum vehicle control group), and 193 were in the PP population (88 in the miconazole nitrate group and 105 in the vehicle control group). Seventy-nine (24%) of the patients who discontinued had clinical evidence of DD complicated by candidiasis at entry but had baseline KOH preparations and/or fungal culture specimens that tested negative. Four patients in the miconazole nitrate group and 58 in the vehicle control group were withdrawn from the study by their caretakers because of clinical failure, worsening, or lack of efficacy. There were no significant differences at baseline between the miconazole nitrate and vehicle control groups with respect to the clinical or mycologic characteristics of DD or demographics with the single exception of patient age, but this was determined not to have affected the validity of the study outcomes (Table). Baseline culture specimens taken from the MITT population tested positive for *Candida albicans* in 97% or more patients, with the remaining culture specimens testing positive for other *Candida*.

Efficacy—On day 14, more patients in the MITT population in the miconazole nitrate 0.025% ointment group than the zinc oxide/petrolatum vehicle control group experienced overall cure

Patient Demographics (Modified Intent-to-Treat Population)

	Miconazole Nitrate 0.25% Ointment (n=112)	Zinc Oxide/Petrolatum Vehicle Control (n=124)	*P* Value
Age, mo			
Mean±SD	7.67±4.87	9.59±6.89	.019*
Range	0.4–24.5	0.6–30.5	
Male, n (%)	51 (46)	57 (46)	.813†
White, n (%)	24 (21)	34 (27)	.384†

*Calculated using analysis of variance with factors of treatment.
†Calculated using a Cochran-Mantel-Haenszel test.

(26/112 [23%] vs 12/124 [10%]; *P*=.005, respectively). Results were similar for overall cure rate in the PP population: 23/88 (26%) versus 7/105 (7%) in the miconazole nitrate and vehicle control groups, respectively (*P*<.001).

A higher percentage of patients in the MITT population in the miconazole nitrate group was clinically cured on day 14 compared with those in the vehicle control group (43/112 [38%] vs 14/124 [11%], respectively; *P*<.001)(Figure 1). Results were similar for the PP population; 38/88 (43%) patients in the miconazole nitrate group were clinically cured compared with 8/105 (8%) in the vehicle control group (*P*<.001). The difference in rates of clinical cure between the miconazole nitrate and vehicle control groups became statistically significant (*P*<.001) by day 7 for both the MITT and PP populations. Only 4/112 (4%) of patients in the miconazole nitrate group withdrew from the study for clinical failure, worsening, or lack of efficacy compared with 58/124 (47%) of patients in the vehicle group for the MITT population.

Both treatment groups had comparable mean DD severity index scores at baseline, and mean scores for both treatment groups decreased during the course of the study (Figure 2). However, the mean scores for patients in the miconazole nitrate group decreased more rapidly from baseline to day 14 and were significantly lower from day 3 through day 14 (*P*<.001). By day 14, the mean DD severity index score decreased 74% from the baseline value (from 5.05 to 1.3) for the miconazole nitrate group compared with a 29% decrease (from 4.98 to 3.52) for the vehicle control group. Results for the PP population showed a greater difference between treatment groups: by day 14, the mean DD severity index score decreased 79% from the baseline value (from 5.2 to 1.1) for the miconazole nitrate group compared with a 27% decrease of (from 4.99 to 3.64) for the vehicle control group. In both the miconazole nitrate and the vehicle control groups, 93% (53/57) of patients who were clinically cured at day 14 remained rash free at day 28.

KOH preparations performed on day 7 tested negative in 89/105 (85%) patients with observations in the miconazole nitrate group compared with 40/111 (36%) of those in the vehicle control group for the MITT population. By day 14, KOH preparations tested negative in 89/99 (90%) patients with observations in the miconazole nitrate group compared with 44/61 (72%) patients in the vehicle control group for the MITT population. Results were similar for the PP population on both study days.

Cultures performed on specimens on day 7 tested negative in 43/112 (38%) patients in the miconazole nitrate group compared with 24/124 (19%) in the vehicle control group for the MITT population. On day 14, for the MITT population, cultures tested negative in 56/112 (50%) patients in the miconazole nitrate group but in only 29/124 (23%) patients in the vehicle control group. Results were similar for the PP population on both study days.

Tolerability—The percentage of patients with adverse events was comparable between groups: 22% for the miconazole nitrate group and 19% for the vehicle control group (*P*=.585). No specific adverse events were observed at a rate of 5% or greater, and the only specific adverse event reported for skin and subcutaneous tissue in the miconazole nitrate group was heat rash in one patient. No reported adverse

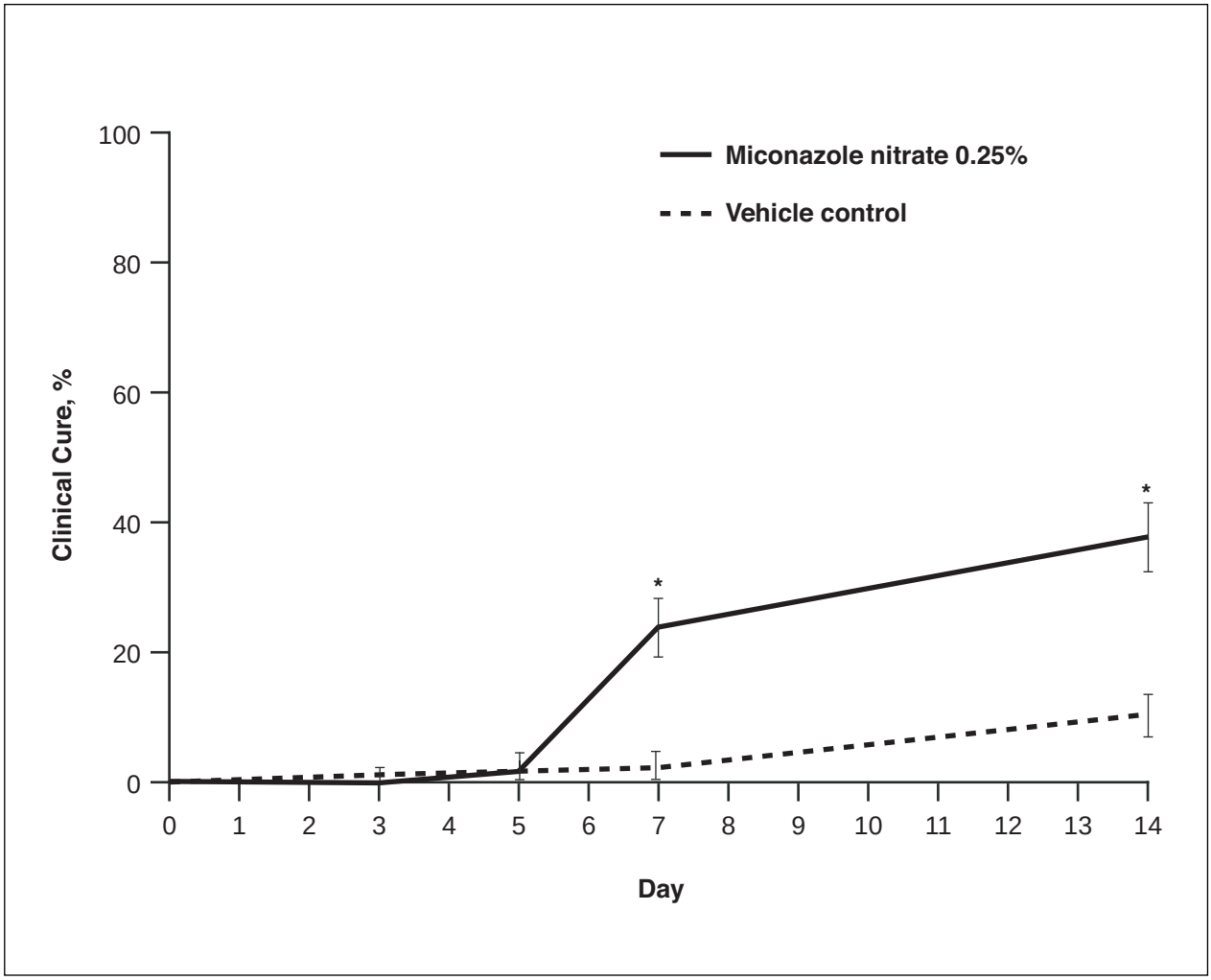

Figure 1. Percentage of patients achieving clinical cure by study day. Asterisk indicates $P<.001$ vs the vehicle control group.

event was assessed to be definitely, probably, or possibly related to study medication. Reported adverse events were assessed as either unlikely to be related to study medication or unrelated to study medication.

Comment

The incidence of DD, especially severe DD, has decreased as a result of advances in technology that have improved the way diapers affect the integrity of the stratum corneum.[10] Nevertheless, DD remains a common problem, with an estimated prevalence of 7% to 35% in the United States.[11,12]

In a study of 100 infants and young children with diaper rash, *C albicans* was isolated from the diaper area in 80% of the cases clinically diagnosed as DD complicated by candidiasis.[13] It is believed that *C albicans*, which is carried in the oral cavity by about 50% of infants[14] and commonly is present in the gastrointestinal tract,[15] colonizes the diaper area via fecal contamination. *C albicans* characteristically is present in the feces of infants and young children with clinically overt candidiasis of the diaper area,[16] and the prevalence of severe rash correlates with the presence and level of fecal *C albicans*.[17] However, not all infants and young children with *Candida* in the stool develop DD, and some with candidal DD do not have *Candida* in the stool.[16,18] *Candida* remain viable on porous fabric surfaces such as 100% cotton for at least 14 days,[19] and skin colonization by *C albicans* significantly ($P=.04$) increases when the skin is occluded with polyurethane film.[20]

The integrity of the stratum corneum and host defenses appears to determine whether candidal infection occurs. Invasion by *Candida* triggers an

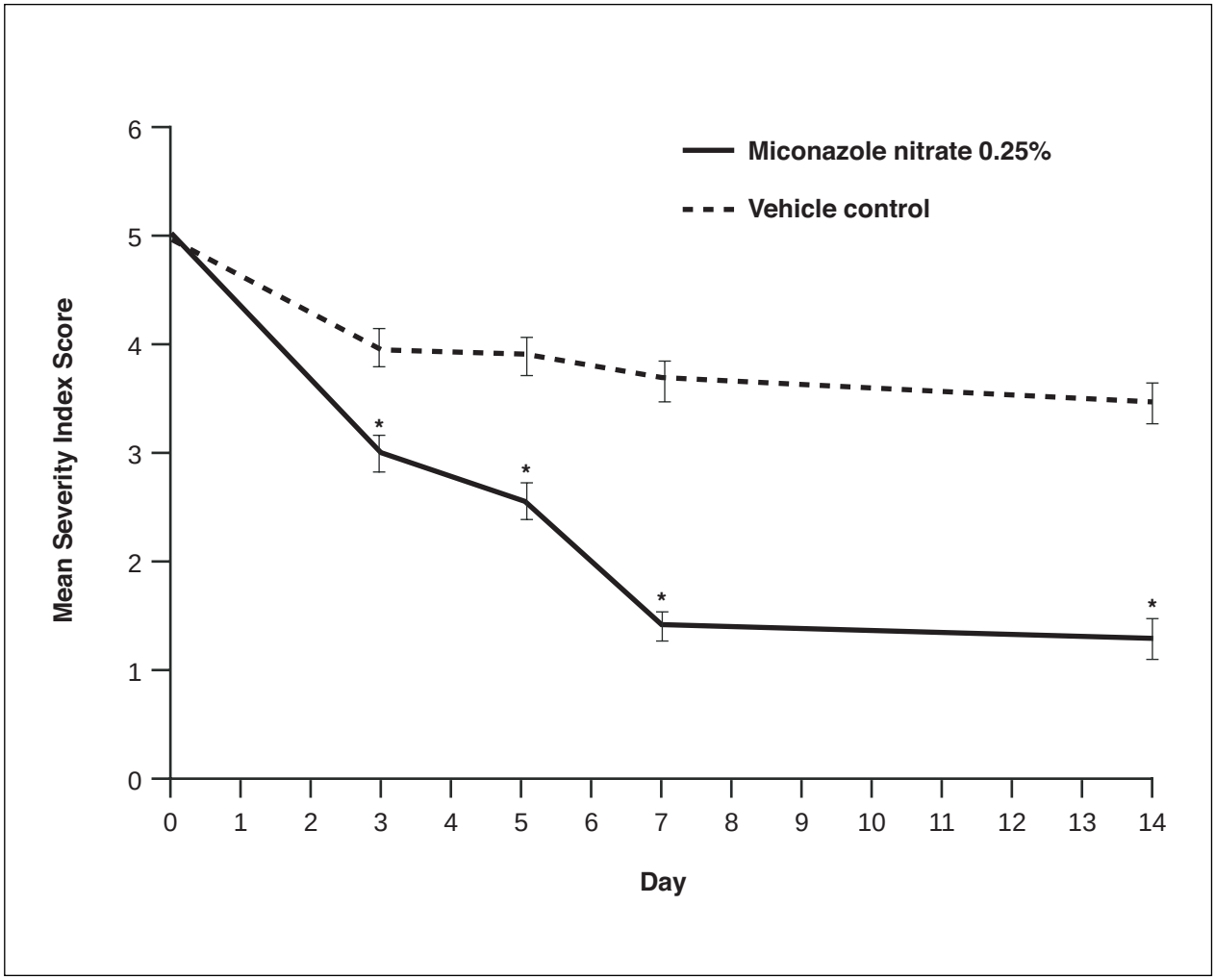

Figure 2. Diaper dermatitis severity index scores from baseline to day 14 for the modified intent-to-treat population. Asterisk indicates $P<.001$ vs the vehicle control group.

inflammatory response that prevents the organisms from invading the skin more deeply. When limited to the stratum corneum, *Candida* is eliminated as the superficial corneocytes are shed. It is possible, therefore, to observe cases of highly inflamed DD that have culture specimens that test negative as a result of the host's immune response. In those who have a poorly cornified epidermis, such as very low birth weight neonates[21] or immunocompromised infants,[22] cutaneous candidal infection may not be limited to the stratum corneum. These organisms then may invade the dermis, leading to potentially life-threatening systemic candidal infections.[23-25]

Zinc oxide has been used for years as a barrier product to treat DD. When applied to the skin, such products both can prevent and treat irritant DD by creating a protective film that shields the skin from maceration by excessive moisture and from injury by fecal enzymes, bile salts, and other irritants.[2,26]

Susceptibility studies have shown that miconazole nitrate 0.25% ointment (equivalent to 2500 μg/mL) markedly exceeds the minimal inhibitory and fungicidal concentrations for *Candida*.[27] In an unpublished study of transdermal absorption of miconazole nitrate 0.25% ointment, plasma concentrations of miconazole through the skin of the diaper area was below the lower limit of detection, 1.0 ng/mL, in the majority (15/18) of patients and was less than 5 ng/mL in 3 patients.[28]

Our study assessed the efficacy and tolerability of miconazole nitrate 0.25% ointment in a subgroup of neonates, infants, and young children with DD complicated by candidiasis. Both the entry criteria and the end points were extremely rigorous. More than one fourth of screened patients with clinical

evidence of moderate to severe DD were not randomized for treatment because of a fungal culture specimen that tested negative. In addition, the FDA required that clinical cure be defined as complete clearing of the rash (defined as a rash score of 0) and overall cure be defined as clinical cure plus negative culture specimens for *Candida* at day 14. Although a proportion of patients in both groups did not meet these rigorous criteria, the overall cure rate for the miconazole nitrate group nevertheless was more than twice that of the vehicle control group for both the MITT and PP populations (P=.005 and P<.001, respectively) at day 14.

In addition, the clinical cure rate was significantly greater (P<.001) for the miconazole nitrate group at days 7 and 14; on day 14, it was greater than 3 times that of the vehicle control group for the MITT population (38% vs 11%; P<.001) and greater than 5 times for the PP population (43% vs 8%; P<.001). If the clinical end point had been a less stringent DD severity index score of 1 or 2 (which is considered a good outcome in actual clinical practice) rather than 0 at day 14, the clinical cure rate for the miconazole nitrate group would have been greater, as suggested by the decrease in severity score (Figure 2). The overall efficacy of the test product is confirmed by the low dropout rate due to clinical failure of the miconazole nitrate group compared with the control group (4% vs 47%, respectively).

The rigorous inclusion criteria of this study required that patients enrolled in the study had both a baseline KOH preparation and a baseline culture specimen that tested positive. However, in everyday practice, most pediatricians who are on the front line of DD treatment usually use visual examination alone to diagnose DD complicated by candidiasis and do not confirm the diagnosis with KOH preparations or laboratory culture specimens. Therefore, by including only those patients with microbiologically confirmed *Candida* infection, the study population may not be fully indicative of patients treated for DD in routine clinical practice.

In neonates, infants, and young children with DD complicated by candidiasis, we found that although the zinc oxide/petrolatum vehicle control appeared to provide some degree of improvement, the miconazole nitrate 0.25% ointment group had significantly greater improvement (P<.001) at day 3, which continued through day 14. Miconazole nitrate showed not only a more rapid benefit but also a more sustained benefit compared with the vehicle control for the treatment of DD complicated by candidiasis. Patients who were considered responders at the 14-day end point had a low risk of relapse because the majority of those reporting back at day 28 were described as cured by their caretaker.

In summary, this study showed that miconazole nitrate 0.25% ointment was well tolerated and significantly more effective than zinc oxide/petrolatum vehicle control for treatment of DD complicated by candidiasis.

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