Cutaneous Candidiasis: Treatment with Miconazole Nitrate

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In a well-controlled, double-blind, randomized study, 30 patients with cutaneous candidiasis were treated with a 2% miconazole nitrate lotion or its placebo control. By the 14th day, 13 of the 15 patients [87%] treated with miconazole nitrate achieved clinical and mycologic cures. Only a single patient treated with the placebo lotion could be classified as a therapeutic cure. In a second portion of the study those patients judged to be therapeutic failures were treated with the lotion containing 2% miconazole nitrate. By combining the results of both portions of the study we find that miconazole nitrate lotion produced both a clinical and mycologic cure in all patients receiving the active lotion. The miconazole lotion formula was well tolerated by all patients and no side effects were noted. The fact that miconazole nitrate acts rapidly in relieving symptoms, is well tolerated, and is highly effective against dermatophytes, yeasts and gram-positive bacteria, makes it a welcome addition to available topical therapy of skin infections.

Miconazole nitrate is a synthetic derivative of phenethylimidazole with topical antimicrobial activity against dermatophytes, yeast, and gram-positive bacteria.1-4 Early European reports of miconazole nitrate's clinical usefulness grouped dermatophyte and yeast infections, making it difficult to ascertain miconazole nitrate's efficacy in controlling cutaneous candidiasis. This study was designed to establish the effectiveness of miconazole nitrate in the therapy of cutaneous candidiasis. This paper reports the results of this well controlled study in patients with proven Candida albicans infection.

Materials and Methods

Thirty patients with cutaneous candidal intertrigo, paronychia or perlèche from the private practice of the investigator were included in the study. Clinical diagnosis was verified by the observation of yeast forms and/or pseudohyphae in scrapings treated with a 20% potassium hydroxide-dimethylsulfoxide mixture5 and/or in smears stained by the Gram technique. Appropriate specimens from all patients grew colonies identifiable as Candida albicans by developing the typical dark brown or black colonies on Nickerson's medium6 and the cream colored, smooth, mucoid colony on dermatophyte test medium (DTM).7 All topical and systemic antiinfective therapy was discontinued at least two weeks before test medication was begun and only the

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test material and a mild, nonmedicated soap were allowed for the duration of the study. The study was divided into two phases. In phase I, patients were supplied with either 2% miconazole lotion or its placebo control. Distribution was accomplished by a randomized technique. Patients were instructed to apply the material twice daily to affected areas. Repeat clinical and mycological evaluations were accomplished after 7 and 14 days of therapy. Patients judged to be therapeutic failures after 14 days of treatment were entered into phase II of the study. In the second phase of the study, patients were treated an additional 14 days with a lotion from coded containers, and evaluated weekly. Patients experiencing clinical and mycologic clearing in phase I were not entered into phase II, but were reexamined at days 21 and 28 to detect any evidence of relapse. All the medication on the phase II part of the study was 2% miconazole nitrate, a fact unknown to the investigator until the code was revealed at the end of the study. This portion of the study was designed by the sponsor to insure that all patients would receive adequate therapy for their disease, while also providing additional information on efficacy and required duration of therapy. No medication was to be applied to the clinically affected areas for at least 12 hours prior to evaluation on days 7, 14, 21 & 28. In those patients not entered into the phase II portion of the study, no treatment of any kind was applied between the end of phase I part of the study and the 28th day follow-up visit.

Results
In phase I, 15 patients received active medication and 15 received the placebo. By day fourteen, 13 of the 15 patients [87%] treated with miconazole nitrate achieved clinical and mycologic cures. The two patients who did not have a complete therapeutic cure in the first two weeks, responded in phase II to the second course of active therapy (Table I and II). No relapses were noted at the 28th day examination in the 13 patients from phase I with therapeutic cures. Symptomatic relief from miconazole therapy was noted within the first 48 hours in 12 of 15 patients in phase I of the study.

In the placebo group, the clinical signs persisted and mycologic tests remained positive in 14 patients. Only a single patient could be classified as a therapeutic cure at day 14 in the placebo group of patients. This patient had interdigital candidiasis of the hand. Phase II medication produced a therapeutic cure in the remaining 14 patients (Table I and II).

Combining the results of patients treated in phase I and phase II, we find that miconazole produced a therapeutic cure in all 29 patients receiving the active lotion. In 27 patients, a cure was obtained within 14 days of active therapy while two patients required additional therapy. The miconazole lotion formula was well tolerated by all of the patients and no side effects were noted.

Commentary
The need for a safe and effective topical antifungal preparation has been intensified by an increased incidence of cutaneous and mucocutaneous candidiasis. Miconazole has been success-

TABLE I: Patients Classified According to KOH, Culture, and Clinical Evaluation at the End of Phase I

<table>
<thead>
<tr>
<th>Miconazole</th>
<th>KOH Result</th>
<th>Neg</th>
<th>Pos</th>
<th>Culture Result</th>
<th>Neg</th>
<th>Pos</th>
<th>Clinical Evaluation:</th>
<th>Good-Excellent</th>
<th>13*</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Fair-No Change</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>KOH Result</td>
<td>Neg</td>
<td>Pos</td>
<td>Culture Result</td>
<td>Neg</td>
<td>Pos</td>
<td>Clinical Evaluation:</td>
<td>Good-Excellent</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>Fair-No Change</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
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</tr>
</tbody>
</table>

*Therapeutic Cures
fully used in the topical treatment of cutaneous and vaginal candidiasis\(^1,8-19\) with greater than 90\% of the patients showing clinical and mycologic clearing. Peeters et al\(^26\) suggested a regenerative effect on Döderlein's bacilli, as well as a normalization of the vaginal pH. By limiting this study to patients with proven *Candida albicans* infection, and studying these patients in a well-controlled, double-blind manner, the therapeutic effect of this broad spectrum, topical antimicrobial agent in cutaneous candidiasis could be established. The cause of the increased incidence of candidiasis is attributed to the widespread use of oral contraceptives, systemic antibiotics, immunosuppressants, as well as to the almost universal use of the less absorbent, heat-retaining synthetic fibers in clothing manufacture. Although most workers agree that there is an increased number of patients with candidiasis, especially vaginal candidiasis, some doubt the relative importance of the often repeated precipitating factors. In a recent study\(^21\) evaluating long-term tetracycline therapy for acne vulgaris, the incidence of vaginal candidiasis was only 1.3\%. In the examination of an unselected group of 453 women with the major symptom of a vaginal discharge, Lohmeyer et al\(^8\) were able to demonstrate *Candida albicans* infection by culture in 15\% of the cases. In a study designed to determine the prevalence of yeast infections as well as the effectiveness of miconazole therapy, Vanheule et al\(^22\) reported an amazingly high incidence of vulvar or scrotal infection, predominantly due to *Candida albicans*, of 20.7\% of 121 premature infants and of 13.2\% of 38 children under the age of six.

The development of such undesirable side effects as permanent atrophic striae in the groin and allergic sensitization by one or more of the multiple ingredients of Mycolog\textsuperscript{®} cream has rendered this widely used combination product less useful than it had been in the past. Miconazole nitrate, 1-(2,4-dichloro-B-(2,4-dichlorobenzyl)oxy)phenethyl]] imidazole mononitrate, was first synthesized in 1969,\(^23\) and has been available in Europe since 1971. The broad spectrum antimicrobial action of this compound against a wide variety of pathogenic organisms has been confirmed in clinical studies.\(^24-27\) When applied locally in guinea pigs with cutaneous candidiasis, miconazole has been found to exert a better effect than amphotericin, nystatin and primaricin.\(^2\) Similar results have been demonstrated in humans.\(^11\) Miconazole appears to act primarily on the yeast cell membranes inducing selective permeability changes.\(^28\) Early European studies suggested that miconazole had antiseptic value, but many of these studies combined dermatophyte and yeast infections under the term "fungal origin", making it difficult to determine the degree of effectiveness against pure yeast infections. Early studies\(^9,31\) tended to have large numbers of patients in which the causative organism was not isolated, therefore leaving doubt as to the correct diagnosis. Miconazole appears to be quite safe as there were no systemic or topical adverse reactions either in this study or in any of those reported in the literature. Miconazole has been reported\(^34,35\) to be effective and non-toxic when used systemically by oral or intravenous administration for systemic candidiasis.

Multiple studies\(^24,25,30\) report very rapid relief of symptoms with miconazole therapy. In fact one investigator\(^30\) suggested that it has a true antipruritic effect. Patients were accordingly questioned concerning the rapidity with which they experienced symptomatic relief. Twelve of the 15 patients who received miconazole in the first part of this study experienced relief of their symptoms within the first 48 hours of therapy.

**Product Information**—Miconazole nitrate: (Johnson & Johnson Dermatologic Division).

**References**