TOLNAFTATE THERAPY OF MYCOTIC INFECTIONS

Preliminary Report*

Harry M. Robinson, Jr., M.D. and Joan Raskin, M.D.

Prior to the introduction of the systemic use of griseofulvin for the treatment of selected superficial mycotic infections, there was no satisfactory method of management available. Although great claims had been made for some of the topical proprietary preparations, at best they were proved to be only palliative, the main virtue being the keratolytic effect produced by them. In spite of the fact that there is a low incidence of adverse reactions to griseofulvin, the problems of photosensitivity, gastrointestinal disturbances, headache, etc. are still encountered. Topically applied griseofulvin, regardless of the excipient used, is of questionable value. It is evident that an efficient topical fungicidal or fungistatic agent with a low incidence of sensitivity reaction would be of inestimable therapeutic value.

During the past ten years, Japanese scientists (1) have assayed more than 3000 topically applied compounds for toxicity and antifungal activity. In 1960 a group of agents with antifungal properties was derived from 0-2-naphthyl-N-methylthionocarbamates. The most promising compound of this group proved to be 0-2-Naphthyl m, N-dimethylthiocarbanilate.

This drug, in two dilutions, one of its congeners, and a control were submitted under blind label for clinical and laboratory investigation. This report contains the results of the preliminary study.

METHODS AND MATERIALS

The drugs: Supplies of four different preparations, in identical plastic containers, labelled A, B, C, and D were delivered for study. The code was contained in a sealed envelope which was not opened until a sufficient number of patients had been treated to allow conclusions to be drawn. The plastic squeeze bottles had narrow openings to permit drop control of the medication. The control used was polyethylene glycol 400, the solvent used for the active agents. Each of the preparations and the control were identical in appearance and consistency.

The major portion of this study was performed with tolnaftate (0-2-Naphthyl m, N-dimethylthiocarbanilate) using dilutions of 1.0% and 0.5%. A congener, 0-2-naphthyl-N-methyl-1-naphthylthiocarbamate, was used in the treatment of 23 patients but study with this compound was discontinued because it proved to be only fungistatic whereas tolnaftate is fungicidal. These compounds are soluble in organic solvents but are virtually insoluble in water. The preparations as dispensed were odorless and colorless.

The toxicity to man on topical application or on oral administration is virtually negligible (1). Tolnaftate proved to be totally ineffective on oral and parenteral administration. In laboratory animals the drug was found to have no pharmacologic action on the cardiovascular apparatus, the central nervous system, or the respiratory apparatus. The results of these studies by Japanese investigators (1) have been confirmed in the United States by similar experiments (2). If percutaneous absorption of tolnaftate does occur, the possibility of organic damage is negligible.

Patient selection: Those included in this study were diagnosed and treated in the out-patient dermatology clinic of the University of Maryland and the authors' private practice. The range in age was from 9 to 70 years. White and Negro patients of both sexes were included.

Treatment was initiated in 96 patients but of this number, seventy five completed the prescribed course. Direct microscopic examinations were positive for hyphae in all patients before medications were prescribed. Cultures on Sabouraud's medium were obtained from all of them at the time of the initial visit, except the six who had tinea versicolor. Culture results from the other sixty-nine patients who completed treatment were as follows:

Trichophyton rubrum	49
Candida albicans	3
Epidermophyton floccosum	2
Trichophyton mentagrophytes	2
Microsporum audouini	1
Contaminated cultures (organism not identified)	12

The twelve patients from whom the twelve contaminated cultures were obtained had clinical lesions of tinea corporis on the trunk.

Both local and disseminated lesions were present in the patients included in this series. The distribution of lesions and diagnoses were as shown in Table 1.

Procedure: After the diagnosis of a mycotic infection was established by direct microscopic examination, a culture was made and the selected medication furnished to the patient with instructions to apply a thin film twice daily to the involved areas with a gentle rubbing motion. Solu-

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* From the Division of Dermatology of the Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland.

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TABLE 1

Number of Patients	Location of Lesions	Culture
14	groins	Trichophyton rubrum
2		Candida albicans
4		Contaminated culture
4	one or both hands	Trichophyton rubrum
10	one or both	Trichophyton rubrum
3	feet	Contaminated culture
2		Trichophyton mentagrophytes
1		Candida albicans
1		Epidermophyton floccosum
11	body or extremities	Trichophyton rubrum
1		Epidermophyton floccosum
2		Contaminated culture
4	toenails or fingernails	Trichophyton rubrum
1	scalp	Microsporum audouini
5	hands and feet	Trichophyton rubrum
1		Contaminated culture
1	groins and	Trichophyton rubrum
2	feet	Contaminated culture
6	tinea versicolor on body	No culture

tion "C", found by clinical trial to be the non-medicated placebo, was given to five patients. When no improvement was noted with solution "C" after one week, solution "B" or "D" was administered. Solution "A", later proved to be the fungistatic congener and subsequently dropped from the study, was prescribed for 23 patients. Three patients in this latter group had recurrence of lesions and were subsequently treated with the "D" solution (0.5% tolnaftate). This solution was also given to 23 additional patients. The "B" solution (1.0% tolnaftate) was used in the treatment of 29 patients. Post-treatment direct microscopic examinations were performed on the 6 patients who had tinea versicolor. Post-treatment cultures were made from the site of prior involvement of the other patients with superficial mycotic infections.

RESULTS

Control study: Five patients with *Trichophyton rubrum* infections of the groins were treated with the non-medicated placebo for one week. No relief of subjective symptoms or change in the appearance of the cutaneous lesions was observed following the use of this preparation (solution "C"). Preparation "B" (1% tolnaftate solution) was used in the treatment of 3 of these patients and preparation "D" (0.5% tolnaftate solution) was administered to the other two. Relief of subjective symptoms occurred in all 5 patients in from 24 to 72 hours and involution of lesions was complete in from 2 to 3 weeks. The "B" and "D" solutions produced identical results.

Tinea versicolor: Four of these patients were treated with "B" solution and 2 with the "D" solution. After a period of 2 to 3 weeks, there was partial to complete disappearance of scale from the lesions but in all instances, in spite of clinical improvement, direct microscopic examination was positive for *Malassezia furfur*.

Monilial infections: One patient with candida albicans infection between the toes was treated with solution "A" (the congener) and 2 patients with candida albicans infections of the groins were treated with solution "B" (1% tolnaftate solution). There was no evidence of clinical improvement in any of these 3 patients after 2 weeks of treatment.

Trichophyton rubrum infections: Sixteen patients with *Trichophyton rubrum* infections were treated with solution "A" (the congener). Six of these had interdigital involvement of the feet, two had lesions on the trunk, three had tinea cruris and two involvement of the toenails. In four other patients who had lesions clinically characteristic of *Trichophyton rubrum* infections, the initial culture was contaminated although the direct microscopic examinations were positive. These patients were also treated with solution "A". After one month of treatment no appreciable change was observed in the toenail lesions and therefore treatment was discontinued. Relief from itching occurred in from 24 to 72 hours in all of the other patients. The interdigital lesions showed improvement in one week and in all instances disappeared in 2 to 3 weeks. Lesions on the trunk, groin and extremities showed marked improvement during the first week of treatment and complete clearing in from 2 to 4 weeks. There was clinical relapse of groin and trunk lesions in 3 patients who subsequently responded to treatment with solution "D". No evidence of irritation or hypersensitivity developed from the use of this solution.

Solution "B" (1% tolnaftate) was used in the treatment of 16 patients with *Trichophyton rubrum* infections. Six additional patients whose initial culture was contaminated but who had clinical lesions characteristic of *Trichophyton rubrum* infections were also treated with solution "B". Relief from itching was prompt in from 24 to 72 hours in all cases. All patients in this group showed some degree of improvement within 7 days and in all instances involution of lesions was complete in from 2 to 4 weeks. After one month of treatment, no improvement was observed in the single case of onychomycosis and because of this treatment was discontinued. No evidence of irritation or hypersensitivity developed from the use of this solution.

Solution "D" (0.5% tolnaftate) was used in the treatment of 17 patients who had positive cultures for trichophyton rubrum and in 2 other patients who had lesions clinically characteristic of *Trichophyton rubrum* infections but whose initial cultures were contaminated. Significant improvement was not observed in the one patient who had onychomycosis and therefore treatment was discontinued. In all of the other patients there was prompt relief from itching in from 24 to 72 hours. Clinical improvement was observed at the end of one week in all instances and complete involution of lesions was observed in 2 to 4 weeks. No evidence of irritation or hypersensitivity was noted. Positive cultures were obtained from 3 of these patients after all clinical evidence of infection had disappeared.

Epidermophyton floccosum: Two patients with *Epidermophyton floccosum* of the feet and trunk were studied. One of these was treated with solution "D" (0.5% tolnaftate) and the other with solution "B" (1.0% tolnaftate). In both instances there was relief from itching in from 24 to 72 hours. Partial involution of lesions occurred in one week and in both instances complete involution of lesions had occurred in 3 weeks. No evidence of irritation or hypersensitivity occurred from the medication.

Trichophyton mentagrophytes infections: Two patients with tinea pedis due to this organism were treated with solution "A". Relief from itching occurred in from 24 to 72 hours and in both instances involution of lesions was complete within 3 weeks.

COMMENT

This preliminary study indicates that tolnaftate, topically applied, is an effective agent for the treatment of superficial mycotic infections due to *Trichophyton rubrum*, *Epidermophyton floccosum* and *Trichophyton mentagrophytes*. The observations recorded reveal no incidence of primary irritation or acquired contact sensitivity. Although the experience is slight, tolnaftate is apparently of no value in the treatment of tinea capitis, or cutaneous lesions due to *Candida albicans*. It is difficult to evaluate this drug in the management of onychomycosis because of the prolonged observation time necessary. During the time of this study, satisfactory improvement was not observed in the nail infections of the four patients treated with topical applications of tolnaftate. Rapid and complete clearing of interdigital fungus infections was noted in all cases treated. In these cases, tolnaftate produced involution of lesions, a result which could not be obtained with systemically administered griseofulvin or keratolytic agents such as undecylenic acid or salicylic acid. In all instances in which itching was a prominent symptom, relief of subjective symptoms occurred in 24 to 72 hours.

This initial report indicates that tolnaftate is a valuable and effective fungicidal agent with a low index of sensitization. Obviously a more extensive study must be done with a larger series of patients. It would be desirable to include in future studies eruptions due to as many of the dermatophytes as possible. Further *in vitro* studies are indicated to determine the spectrum of tolnaftate and its mode of action.

CONCLUSIONS

1. Tolnaftate (0.5% and 1.0% in polyethylene glycol 400) is an effective agent in the treatment of superficial mycotic infections due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*, and produces rapid clearing of interdigital infections due to these fungi.

2. This drug is of no value in the treatment of *Candida albicans* infections, in the management of tinea capitis, and of questionable value in tinea versicolor.

3. More intensive study and different technic are required to determine its value in onychomycosis. Satisfactory results were not obtained in the present study.

4. No evidence of primary irritation or hypersensitivity was observed.

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