
Ketoconazole in griseofulvin-resistant dermatophytosis

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The efficacy of ketoconazole was evaluated in twenty patients with chronic dermatophyte infections who had failed to clear with griseofulvin therapy. *Trichophyton rubrum* was the causative organism in nineteen of the patients, and *Trichophyton mentagrophytes* in one patient. Three of twelve organisms tested showed in vitro resistance to griseofulvin. Duration of infection ranged from 2 to 28 years. Patients received 200 to 400 mg of ketoconazole daily for periods up to 8 months. In addition, patients were followed for 5 months post-therapy to monitor recurrences. Clearing was seen clinically as early as 2 weeks, and by 18 weeks all patients showed marked improvement or clinical clearing, though only six achieved complete mycologic cure. Improvement followed a predictable sequence of sites, with lesions of the trunk healing first, followed by hands, feet, and finally, nails. After 8 months, though all patients showed proximal nail clearing, onychomycosis persisted in thirteen of twenty affected sites. By 5 months post-therapy, four of six patients who had achieved clearing of skin and nails showed recurrences. No significant side effects were observed during therapy, though rare, apparently idiosyncratic cases of hepatotoxicity have been reported. Ketoconazole is an effective therapeutic agent for griseofulvin-resistant dermatophytosis. Apparent cures may subsequently recur after discontinuation of therapy. (J AM ACAD DERMATOL 6:224-229, 1982.)

Ketoconazole is a new oral antifungal agent. Studies demonstrate a broad spectrum of activity against superficial and deep mycoses.¹

Previously, griseofulvin was the only available oral antifungal effective against dermatophytes. Treatment failures and recurrences have frustrated patients and clinicians. In 1960, Goldfarb and Sulzberger² and Prazak et al³ independently re-

ported on tinea pedis patients treated with 6- to 20-week courses of 250 to 1,000 mg of griseofulvin daily. Of the sixty-six patients treated by Goldfarb et al, only thirty-eight (58%) clinically cleared and had negative cultures. Of the twenty "cured" patients seen at follow-up visits, twelve (60%) had recurrences. Prazak et al had similar experiences, with only twenty-five of sixty-three patients achieving a cure. Ten of these twenty-five patients showed recurrences at follow-up visits.

Ketoconazole, like miconazole and clotrimazole, is an imidazole. It is distinguished from other imidazoles by the presence of a piperazine ring. Ketoconazole inhibits the biosynthesis of er-

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gosterol. Specifically, the demethylation of lanosterol is blocked, resulting in leaky membranes. The concentration necessary to inhibit mammalian sterol synthesis is 600 times that necessary to inhibit fungal sterol synthesis.⁴ The drug is metabolized in the liver and has relatively poor central nervous system absorption.

Our objective was to study the efficacy and toxicity of ketoconazole in patients who remained infected after their dermatophytosis had been treated by griseofulvin.

PATIENTS

We deliberately selected difficult patients in terms of the chronicity of their infections and their lack of success with prior therapies.

Seventeen of the twenty patients had chronic dermatophytosis, as documented in clinical records, of 5 to 28 years' duration. Three of the twenty patients had clinical documentation of infection for only 1 year's duration, but had been symptomatic for longer periods of time. Sixteen had severe onychomycosis in addition to their glabrous skin infections.

Eighteen of the twenty patients had previous treatment equivalent to, or exceeding, 500 mg of griseofulvin ultrafine for at least 4 months. One patient was intolerant of griseofulvin because of nausea. One patient had used only topical antifungals, but was entered into the study because of extensive urticaria thought to be secondary to tinea pedis.

Eighteen patients used topical antifungals prior to entry into the study. Most of these had used multiple treatments either alone or in combination with griseofulvin. Topicals used included: haloprogin, six patients; miconazole, ten patients; tolnaftate, seven patients; and clotrimazole, three patients.

All patients continued to be symptomatic in spite of the preceding therapies. Each had initially responded to griseofulvin therapy but later became unresponsive. In addition, *in vitro* testing of dermatophytes from twelve patients studied by Dr. William Artis revealed three resistant to griseofulvin in culture. These organisms grew in liquid culture in the presence of normally inhibitory concentrations of griseofulvin, with minimal inhibitory concentrations (MIC) of 5, 18, and 3 $\mu\text{g}/\text{ml}$, respectively. In this assay system, resistance is defined as $\text{MIC} \geq 3 \mu\text{g}/\text{ml}$.⁵ These three patients had infections for 9, 25, and 28 years, and all had been treated intermittently with griseofulvin for over 5 years. They had a complete lack of clinical response to a standard course of griseofulvin and also failed to clear on higher dos-

ages of 2.5 gm griseofulvin, as measured by gas chromatographic determinations of griseofulvin in serum and skin.*

METHODS

Potassium hydroxide microscopic examination (KOH) and culture confirmed fungal infection in each patient. Complete blood count, urinalysis, and chemistry screen (serum sodium, potassium, chloride, phosphate, calcium, glucose, urea nitrogen, protein, bilirubin, cholesterol, alkaline phosphatase, lactic dehydrogenase and serum glutamic oxaloacetic transaminase [SGOT]) were obtained prior to initiating therapy, and monthly thereafter. Patients received 200 mg of ketoconazole daily. If clinical response was judged to be slow at 1 month, dosage was increased to 400 mg daily. Patients were evaluated at 2 and 4 weeks and then monthly for up to 8 months. Clinical assessments included recording all sites of obvious disease as to degree of scaling, maceration, and inflammation. A comparison with the pretreatment clinical status was recorded as either (1) no improvement, (2) slight to moderate improvement, (3) marked improvement, or (4) clinically clear. In addition, a KOH was performed at each site of current or previous clinical involvement. If the KOH was negative, a culture was planted to rule out subclinical infection. Treatment was discontinued 1 month after skin and nail involvement was clinically clear and mycologically negative.

RESULTS

Nineteen of our twenty patients were infected with *Trichophyton rubrum* and one patient with *Trichophyton mentagrophytes*. Two patients had tinea versicolor in addition to their dermatophytosis.

All patients showed clinical improvement within 10 to 60 days. Truncal lesions cleared most rapidly, followed by hands and then feet and nails.

Table I shows the course of glabrous skin responses to ketoconazole therapy. One patient cleared by 2 weeks, and all but one showed improvement by the second visit at 6 weeks. Clearing progressed sequentially, such that by 14 weeks 75% of patients were clinically clear.

Three patients retained residual scaling by the end of 8 months, but eleven of twenty patients remained mycologically positive on glabrous skin

*Hanifin JM, Shah V, Riegelman S: Unpublished data.

Table I. Clinical responses of glabrous skin dermatophyte infections to ketoconazole therapy

Patients showing	Evaluation time (wk)					
	2	6	10	14	18	32
No improvement	11	1	0	0	0	0
Slight/moderate improvement	5	10	3	0	0	0
Marked improvement	3	8	10	5	3	3
Clinically clear	1	1	7	15	17	17

Table II. Eight-month assessment of therapeutic response to ketoconazole of regional dermatophyte infections

Body region	Clinically clear	KOH-negative	Culture-negative
Trunk	4/4	4/4	4/4
Hands	10/11	10/11	10/11
Feet	6/19	9/19	8/19
Fingernails	8/9	8/9	8/9
Toenails	4/16	4/16	3/16

in spite of being clinically clear. Cumulative results at the end of the 8-month treatment study are shown in Table II.

The four patients with tinea corporis became clinically clear and culture-negative after 2 months of ketoconazole therapy, at which time treatment was discontinued. Two were infected with griseofulvin-resistant organisms. Another patient's infecting organism showed in vitro sensitivity to griseofulvin, while the fourth patient's was not tested. None of these patients had responded clinically to griseofulvin.

Ten of the eleven patients with tinea manus were clinically clear and culture-negative after 8 months of therapy. Nine of these patients had fingernail infections that cleared as well. The one patient failing to achieve a cure showed marked clinical clearing but continued to be KOH-positive.

Nineteen patients had tinea pedis. Sixteen of these patients also had onychomycosis of the feet. The skin of the feet appeared clinically clear in sixteen of these patients, and all showed marked improvement. However, only nine were KOH-negative and only eight were culture-negative. This illustrates the importance of using fungal cultures rather than clinical response as an end point

to therapy. All patients with onychomycosis of the feet showed proximal nail clearing, but only three were culture-negative after 8 months of therapy.

The two patients with tinea versicolor cleared by the 2-week visit. The patient with urticaria cleared by the 2-week visit and had no further episodes of urticaria, though mycologic clearing was not recorded until 10 weeks.

POST-TREATMENT FOLLOW-UP

Six patients achieved total clearing of all glabrous skin and nails after 8 months on ketoconazole therapy. Clinical data on these six patients are outlined in Table III. After 4 to 7 months post-therapy follow-up, four of six patients had recurrences. The sites of most obvious clinical involvement on follow-up visits were frequently the first sites to have cleared. For example, Patient 14 cleared his tinea corporis after 2 months on ketoconazole therapy, but the initial clinical recurrence was tinea corporis rather than slower to clear areas of the hands and feet.

SIDE EFFECTS

Side effects were minimal during ketoconazole therapy. Six patients experienced nausea when ketoconazole was taken on an empty stomach.

Table III. Case summaries of patients clinically and mycologically cured by ketoconazole

Patient	Age	Duration of dermatophytosis (yr)	Sites	Prior therapy	Ketoconazole therapy (wk*)	Recurrence†
3	29	9	H,F	Hp,M,Gf	16	Yes, 7 wk
8	32	10	F,Tn	M,Gf	4	Yes, 8 wk
7	39	5	G,B	C,Gf	2	None
12	26	9	F,G,G, Tn,Fn	T,M,C	16	4 mo
14	43	16	F,G,G,Tr Tn,Fn	M,Gf	8	Yes, 5 wk
17	36	6	F	T	8	Lost to follow-up

B: Buttocks; C: clotrimazole; F: feet; Fn: fingernails; Gf: griseofulvin; G: groin; Hp: haloprogin; H: hands; M: miconazole; T: tolnaftate; Tn: toenails; Tr: trunk.

*Weeks of ketoconazole therapy until culture-negative.

†Time after discontinuing ketoconazole therapy to mycologic recurrence.

This was easily eliminated by medicating with meals. This did not appear to affect patient responsiveness to therapy.

Two patients had single episodes of epistaxis during the first month of therapy. Both patients reported intermittent epistaxis related to allergic rhinitis prior to initiating ketoconazole therapy. One patient complained of glare from headlights and photophobia in the early morning light. Complete ophthalmologic examinations on two occasions failed to disclose an explanation for this complaint. No laboratory abnormalities appeared during therapy.

DISCUSSION

Dermatophyte treatment failures are more common than generally appreciated. The cause of such failures remains unclear. Theories explaining the persistence of infection despite "adequate" therapy include:

1. Inadequate treatment (secondary to inadequate dose or duration of therapy, malabsorption, decreased skin delivery, hypercatabolism)
2. Reinfection (from fomites, from housemates)
3. The development of a resistant organism
4. A specific immunologic deficit peculiar to the host
5. Lack of a fungicidal agent

Inadequate treatment most often occurs when patients fail to comply with the medication

schedule or when the physician prematurely misinterprets a "cure." Achieving a clinical cure often requires months of therapy, especially when onychomycosis is present. A patient may appear clinically clear and even KOH-negative prior to becoming culture-negative. Premature discontinuation of medication results in persistent infection and recurrence of clinical symptoms. Some patients, including those in this study, never become culture-negative on griseofulvin or ketoconazole. These patients uniformly had severe onychomycosis of the feet.

The role of reinfection in the course of chronic dermatophyte infection is unknown. Griseofulvin and ketoconazole are static antifungals acting only on growing mycelia. Dormant hyphae may persist through treatment to serve as a source of reinfection after treatment is stopped. The nails and the cleft between the fourth and fifth toes may serve as a reservoir for organisms. These sites may be more resistant to therapy.⁶

The prevalence of resistant organisms in persistent infections has, in the past, been difficult to assess because of technically inadequate assays.^{7,8} Mycelia inactivate griseofulvin in vitro via demethylation. A complicating factor in determining minimal inhibitory concentrations of antifungals in solid media is "stolon-like" hyphal growth.⁹ This refers to the tendency of some dermatophytes to continue aerial extension, with only a few

hyphae serving as "roots" in an inhibitory medium. Antibiotic is not delivered into the hyphae. Thus, hyphae not directly in contact with the media are not subject to inhibition. Achieving consistent standard inoculum quantities has also impaired *in vitro* resistance studies.

The recently developed methodology used by Artis and colleagues⁵ has resolved many of the problems with resistance studies. An inoculum is produced by growing the fungus in a shallow nutrient broth culture. This is then homogenized and the inoculum is standardized spectrophotometrically and added to microcultures containing varied dilutions of the antimycotics. Growth is monitored visually and can be detected within 48 hours.

The correlation of *in vitro* resistance to griseofulvin with clinical responsiveness to therapy is currently being explored. Guinea pigs inoculated with resistant and nonresistant strains responded equally well to griseofulvin treatment in a study by Rosenthal and Wise.⁸ However, they used solid media without attention to "stolon-type" growth. Medoff and Kobayashi¹⁰ recently commented on the similarly poor correlations of amphotericin B *in vitro* susceptibility studies and clinical responsiveness of patients.

Our patients were clinically unresponsive to griseofulvin. *In vitro* resistance correlated well with the lack of clinical responses in a few patients. Unfortunately, *in vitro* studies prior to griseofulvin therapy do not exist. These would aid in determining whether the initial infecting strain possessed the same degree of resistance. The decreasing clinical response in some patients on griseofulvin therapy would indicate that the resistant organism evolved or was selected by the therapy.

Among theories of causality for persistent infections is that of a selective immunologic deficit in affected patients.^{11,12} This is probably unaltered by griseofulvin or ketoconazole therapy. Thus, the patient is always at risk and susceptible to fungal infections when off medications. There is insufficient evidence available to confirm or deny this hypothesis.

Most clinically resistant organisms are slow-growing (e.g., *T. rubrum* and *Epidermophyton floccosum*) and produce very little inflammation. These infections are rarely associated with tricho-

phyton-delayed hypersensitivity.^{11,13} All but one of our patients were infected with *T. rubrum*. Lack of cell-mediated immune response may allow the organisms to grow unimpeded, and the lack of inflammation decreases the shedding of keratinocyte-containing stratum corneum. If the organism can grow peripherally faster than the infected squames can be sloughed, the infection continues.

This communication represents a final report on a group of patients presented in preliminary form previously.¹⁴ Our data can be contrasted with several other early reports of ketoconazole efficacy in dermatophytosis.¹⁵⁻¹⁷

Our results with nail infections were considerably less impressive than those of Galimberti et al.¹⁷ Jones et al treated twenty patients with severe infections which had failed to respond to griseofulvin¹⁶ and/or topical antifungals. Although seventeen of their patients had onychomycosis, the duration of therapy was limited to 2 months, and the effect of ketoconazole on nail infections was not assessed. Thirteen of the twenty patients (65%) were designated clinically clear after 1 months' treatment with ketoconazole. In contrast, after 10 weeks, only 35% of our patients were clear. These differences are not totally explainable, though such subjective evaluations in open clinical trials will necessarily have wide variations. Recurrences in both studies were very high, and this verifies the fact that relatively few of these severe, chronically infected patients can be cured with ketoconazole.

Our studies show that ketoconazole is effective against dermatophytes and that it provides considerable clinical improvement in patients unresponsive to griseofulvin.

Ketoconazole has good patient acceptance, with few side effects. Unfortunately, instances of rare, apparently idiosyncratic liver toxicity from ketoconazole have recently emerged. Changes have been asymptomatic, manifested by varied liver enzyme elevations and documented in one case by liver biopsy.* Enzyme abnormalities have disappeared in every case after cessation of therapy. The incidence can presently be only roughly estimated at between 0.1% and 1.0%.

Until more is known of the liver toxicity,

*Svejgaard E: Personal communication, December, 1980.

ketoconazole cannot be recommended as a first-line drug for dermatophytosis. The drug may provide an alternative method of treatment to abate symptomatology in patients with dermatophyte infections unresponsive to currently available drugs. Stopping the drug may result in recurrence of disease, particularly when there is onychomycosis. Studies of maintenance therapy with reduced or intermittent dosing may provide methods for preventing recurrence in susceptible individuals.

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