

# EVALUATION OF KETOCONAZOLE AGAINST GRISEOFULVIN IN THE TREATMENT OF DERMATOPHYTES

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## SYNOPSIS

The efficacy of Ketoconazole against Griseofulvin was evaluated in 100 patients for treatment of dermatophytosis. 50 patients were treated with a single daily dose of 200 mg Ketoconazole. An equal number of patients were given 500 mg of Griseofulvin in 2 doses. In both, the duration of therapy was 4 weeks.

The remission rate at 4 weeks was observed to be same with Ketoconazole and Griseofulvin (88%). However, they did not clear with further doses of Griseofulvin while a further 4 patients cleared with further treatment with Ketoconazole.

The proportion of relapses at the end of 3 months was lower in Ketoconazole (14%) than in the Griseofulvin group (28%).

The overall results showed a better result with Ketoconazole compared to Griseofulvin. The remission rates are Ketoconazole 82% to Griseofulvin 60%.

The side effects were minimal and present in 6 cases of Ketoconazole, namely breathlessness, giddiness, and headache. 3 patients on Griseofulvin complained of nausea and found to have gastritis.

## INTRODUCTION

Dermatophytosis in Singapore has generally been treated with topical antifungal agents and systemic griseofulvin. With the availability of a new oral imidazole, Ketoconazole, a choice between 2 drugs is offered. The choice will depend on the efficacy and possible side effects encountered with Ketoconazole as compared to the longer established therapy with Griseofulvin (1). Ketoconazole is found to have a broader spectrum of activity than Griseofulvin and offers an alternative in Griseofulvin resistance infections. The drug is presumed to act by inhibiting the 14 $\alpha$  demethylation of lanosterol, precursor in synthesis of ergosterol, the principal sterol in fungal cell membrane and is essential to the integrity of the fungal cell wall (2, 3, 4)

The purpose of the study is to investigate the efficiency and safety of Ketoconazole compared to Griseofulvin in the treatment of dermatophytosis in an Asian country.

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**MATERIALS AND METHOD**

A total of 100 patients with dermatophytoses were selected to this trial with equal numbers for Ketoconazole and Griseofulvin. All patients with onychomycosis and candidiases were excluded. Children and pregnant women were excluded.

Before starting therapy, dermatologic history of duration of the fungal infection, and treatment was taken and examination to assess the extent of fungal infection. A direct mycological microscopic examination (with Potassium hydroxide) and a culture (in Saubouraud's medium) were taken. Biochemical tests were not done as previous studies had shown both to be fairly safe. Care was taken not to include patients with a history of jaundice or hepatitis.

Ketoconazole was given as a single dose of 200 mg at the beginning of a meal, and Griseofulvin 500 mg after a meal.

Response to therapy was assessed fortnightly, evaluating:

- a the decrease in symptoms like pruritis, inflammation and scaling;
- b clinical improvement of extent of dermatophyte infection; and
- c microscopic examination and fungal culture.

A clinical cure would be supported by a decrease and disappearance of the symptoms and signs, though the post-inflammatory discolouration would take a longer time to recover.

The final assessment includes:

- a complete cure: a full clinical, mycological and cultural disappearance of the fungus;
- b clinical cure with residual lesions;
- c no change;
- d deteriorated; and
- e unevaluable.

**RESULTS**

**Clinical data:**

**Sex-age-race incidence**

There were 50 patients in each of the groups that were on Ketoconazole and Griseofulvin. In the Ketoconazole group, there were 39 male and 11 female patients, and their mean age was 35 years (range 15–72). 13 patients were above the age of 50 years. Of these patients, there were 28 Chinese, 25 Malays and 20 Indians.

In the Griseofulvin group, there were 37 males and 13 females. The average age was 34 years (range 14–79). More elderly patients were noted; that is, 21 patients. There were 32 Chinese, 26 Malays, 14 Indians (Table 1). Both the groups showed a higher incidence of fungal infection in the Malays and Indians when compared to the general population where 78% are Chinese, 14% Malays and 8% Indians.

**Concurrent Conditions**

15 patients of the Ketoconazole group had concurrent conditions. Of these, 3 had diabetes mellitus, 3 eczema, 2 asthma, 1 urticaria, 1 tylosis on topical steroids, 1 acne, 1 rosacea. Eleven patients in the Griseofulvin group had these medical conditions: 2 diabetes mellitus, 4 eczemas, 1 asthma, 1 gastritis, 1 herpes zoster and 2 hypertension (Table 2). None of these patients had immunological diseases like lupus erythematosus, chronic myocutaneous candidiasis. None was on oral steroid.

**Antifungal Medication**

In both groups, many patients had used both topical and systemic antifungal medications. Systemically, 19 patients

**Table 1. Clinical Data On 100 Patients Of The Study**

Data	On Ketoconazole	On Griseofulvin
1. Male:Female	39:11 (3:1)	37:13 (3:1)
2. Racial difference Chinese:Malay:Indian:Others	28:25:20:2	32:26:14:1
3. Average Age and range Above 50 yrs	35 yr (15 – 72 yrs) 13 pt	34 yr (14–79 yrs) 21 pt

Table 2. Associated Medical Illnesses In Patients

Disease	Ketoconazole	Griseofulvin
Diabetes Mellitus	3	2
Eczemas	3	4
Asthma	2	1
Urticaria	1	—
Tylosis (with topical steroid)	1	—
Gastritis	—	1
Herpes Zoster	—	1
Hypertension	—	2
Acne	1	—
Rosacea	1	—
	15	11

had been on Griseofulvin before and of these, 14 (73%) of them subsequently were cured on Ketoconazole. 12 patients using Griseofulvin had been treated with the same drug before. Later, only 4 (33%) were cured with Griseofulvin.

Topical therapy had been tried in the Ketoconazole

group, 34 patients (68%) and the of the Griseofulvin group, 27 patients or 54%. These medicaments included Whitfield ointment, a common agent; Daktarin cream and Chinese medication. The latter often contained Salicylic acid and dithranol. Even steroid cream was used as the fungal infection was misdiagnosed (Table 3).

Table 3. Previous Therapy Used By Patients

Therapy	Patients on Ketoconazole	Patients on Griseofulvin
Oral Griseofulvin:	19 pt (38%)	12 pt (24%)
Response in trial	14 cured (73%)	4 cured (33%)
Topical Therapy:	34 (68%)	27 (54%)
Ung Whitfield	22	16
Daktarin	2	1
Chinese medication	3	3
Creams? name	7	6
Steroid cream	2	1

**Site of Infection**

The most common site were Tinea Cruris, about 27 patients in either group, followed by Tinea Corporis 22-23 patients and these were extensive. One patient with Tinea Manuum was treated with Ketoconazole (Table 4). The average duration of the fungal infection was 1.7 years.

**Response to Therapy**

At the end of treatment at 4 weeks, 44 patients treated with 200 mg Ketoconazole/day demonstrated clinical and mycological cure (88%) and 6 showed clinical improvement with mild residual lesions (12%). None showed no re-

sponse and no one discontinued therapy.

A similar result was seen with that of patients on Griseofulvin. There were 44 clinical and mycological cures (88%) and 6 (12%) of mild to marked residual lesions (Table 5).

**Follow-Up till 12 weeks**

The 6 patients who showed clinical improvement on 4 weeks of Ketoconazole, continued their therapy and a further 4 achieved clinical and mycological cure. The other 2 failed to clear despite a full 12 weeks of Ketoconazole and had residual lesions with positive mycological cultures. Seven patients (14%) relapsed within the follow-up period. Overall, there was a 82% complete mycological cure.

**Table 4. Extent Of Fungal Infection**

	On Ketoconazole	On Griseofulvin
1. Tinea Corporis (Extensive, 30%)	19 pt	22 pt
Tinea Corporis (localised)	3	1
2. Tinea Manuum/pedis	1	0
3. Tinea Cruris	27	27

**Table 5. Results Of Treatment Of Patients With Ketoconazole vs Griseofulvin**

Period	Ketoconazole	Griseofulvin
<b>At 4 weeks</b>		
Clinical improvement	6	6
Complete mycological cure	44 (88%)	44 (88%)
<b>At 12 weeks</b>		
Relapses	7	14
Clinical improvement	2	6
Complete mycological cure	41 (82%)	30 (60%)

Compared to ketoconazole, the 6 patients with clinical improvement continued to be mycologically positive despite continuation of Griseofulvin up to 12 weeks. In this group, a further 14 cases (28%) relapsed. This gives an overall mycological cure of 60% at the end of 12 weeks and compared poorly with the 82% cure from Ketoconazole (Table 5).

### Side Effects

Two patients on Ketoconazole complained of breathlessness and drowsiness. None of the patients developed jaundice. Laboratory tests were not performed. Three patients on Griseofulvin complained of drowsiness, headache and pruritis (Table 6).

### Organism

In Singapore, the commonest figure is *Trichophyton mentagrophytes*, followed by *Trichophyton rubrum*, then *Epidermophyton floccosum*. This pattern is reflected in this study.

In the group on Ketoconazole, 23 of 29 cases of *Trichophyton mentagrophyte*, 12 of 14 cases of *Trichophyton rubrum*, 3 of 4 cases of *Trichophyton tonsurans* and all of *Epidermophyton floccosum* achieved complete mycological cures. Relapsed cases include 5 cases of *T. mentagrophytes*, 1 of *T. rubrum* and 1 of *T. tonsurans*. The 2 clinical cure cases include *T. mentagrophyte* and *T. rubrum*.

With Griseofulvin, the 14 relapsed cases include 8 *T. mentagrophyte*, 4 *T. rubrum* and all the *T. tonsurans*. The cases achieving clinical cures include 3 *T. mentagrophyte*, 2 *T. violaceum* and 1 *T. rubrum*. (Table 7)

**Table 6. Adverse Reactions Of Ketoconazole vs Griseofulvin Treatment For Dermatophytosis**

Reaction	Ketoconazole	Griseofulvin
Drowsiness	1 case	1 case
Breathlessness	1 case	
Headache		1 case
Pruritis		1 case

**Table 7. Overall Results Of Ketoconazole vs Griseofulvin Treatment By Pathogenic Organism**

	Ketoconazole				Griseofulvin			
	Remission	Failed	Relapse	Total	Remission	Failed	Relapse	Total
T. Mentagrophyte	23	1	5	29	19	3	8	30
T. Rubrum	12	1	1	14	9	1	4	14
T. Tonsurans	3	0	1	4	2	—	2	4
T. Violaceum	—	—	—	—	—	2	—	2
E. Floccosum	3	—	—	3	—	—	—	—
<b>Total</b>	<b>41</b>	<b>2</b>	<b>7</b>		<b>30</b>	<b>6</b>	<b>14</b>	

Table 8. Series Of Studies Of Ketoconazole

	Jolly (7)	Degreef (8)	Robertson Haniffin et al (9)	Jones (10)	Cox (11)	Welsh (6)	Robertson, Haniffin Parker (15)	Legendre (5)	Rajan
No. of Patients	66 pts	9 pts	20 pts	19 pts	19 pts	33 pts	21 pts	21 pts	50 pts
Types of Fungus	T. Rubrum (45) T. Tonsurans (10) E. Fioccosum (3) Microsporium (1) Others (7)	T. Rubrum (7) T. Mentia (1) T. Verrucosum (1) (T. Pedis mainly)	T. Rubrum (19) T. Mentia (1) (T. Pedis mainly)	recalcitrant cases	Griseo-fulvin resistant	T. Rubrum (19) T. Mentia (4) T. Tonsurans (5) M. Canis (5)	recalcitrant cases	T. Rubrum	T. Mentia (23) T. Rubrum (12) E. Fioccosum (3) T. Tonsurans (3)
Cure	61% 2-16 wks	100% 1 wk - 3 months	100% (dermal) up to 8 months	90% 4 weeks - 2 1/2 months	63% -	53% 1 month	66% 1 month	76% 1 - 2 months	88% 1 month
Follow up - Relapse	9% 2 months	5% 7 months	30% 5 months	75% 5 months	38% 12 pts 1-14 mths	Nil	60% 2 - 6 months	7% 1 month	14% 3 months

Key: T. Mentia: Trichophyton Mentagrophyte

## DISCUSSION

The results of the study appeared to be consistent with those workers of other studies using Ketoconazole in the treatment of dermatomycoses (Table 8). Each study, however, had numerous variables in patient population, site of fungal infections, type of fungus, dosage schedule and duration of treatment. Thus an overall global assessment of the effectiveness of the drug is difficult to make. However, the remarkable efficacy of Ketoconazole seems to be stressed, especially in Griseofulvin resistant cases, and in other recalcitrant and recurrent cases of onychomycoses.

Some of the interesting features in this study is that of the racial differences and associated diseases. The Malays and Indians show an increased incidence of mycoses compared to the population figures. It is wondered whether cultural habits and diet had encouraged spread of these mycoses. The usual associated diseases mentioned by workers were seen in our study, eg asthma, eczemas, tylosis and diabetes. The study does not have many cases of T. lymphocytes deficiency cases.

The study shows that the effect of Ketoconazole compared to Griseofulvin for the treatment of uncomplicated dermatomycoses is similar. With the four weeks of treatment, both drugs showed 44 patients (88%) to be mycologically cured and 6 patients (12%) showing clinical improvement. This gives an 88% total cure. Compared to the others, this is good. Legendre (5) in his double blind study of Ketoconazole to Griseofulvin found a 76% cure with Ketoconazole and his study consisted mainly of T. rubrum cases and were treated for 1–2 months.

Welsh (6), treated 33 patients with Ketoconazole, the fungal patients had a variety of dermatophytes like T. rubrum (19 cases); T. mentagrophyte (4 cases); T. tonsurans (5 cases) and Microsporum canis (5 cases). The cases were treated for a month, with a cure rate of 53%. Jolly (7), also had a lower cure rate of 61% in 66 patients in a double blind study, treated for 2 to 16 weeks. Dageef (8) treating 9 cases of Tinea pedis, with 7 cases T. rubrum, 1 of T. mentagrophyte and 1 T. verrucosum gave a surprising 100% cure at the end of 3 months.

In this study, there were 14 patients (73%), who improved on Ketoconazole, who previously had been on Griseofulvin. This result was not noticed in the patients in the Griseofulvin group which gave a cure in 4 patients (33%) only (Table 3).

This will now be compared with the results of Ketoconazole of others used in recalcitrant cases, the majority being T. rubrum, Ketoconazole was tried in 19 cases by Robertson (9), up to 8 months. The results of mycological cure was 100% in the skin sites though onychomycosis persisted in some. Jones (10) gave a result of 90% mycological cure in 20 cases of T. rubrum treated for 4 weeks to 2½ months. Lower results were obtained by Cox (11), who had 63% mycological cures in treating 19 recalcitrant cases. These figures seem to show that Ketoconazole is at least equal to and probably superior to Griseofulvin in achieving clinical and mycological cures in dermatophyte infection and a better response to recalcitrant cases.

Our study with ketoconazole include T. mentagrophyte (23 cases), T. rubrum (12 cases), E. floccosum (3 cases) and T. tonsurans (3 cases). Follow-up for 3 months showed 14% relapsed rate (7 cases). These include T. mentagrophyte (5 cases), only 1 case of T. rubrum and 1 case of T. tonsurans. The 2 cases (4% who had not been cleared

consisted of 1 T. mentagrophyte and 1 T. rubrum).

Compared with Griseofulvin, the relapse rate is doubled 28% and 12% of cases had not been cured on it. Of a total of 30 cases of T. mentagrophyte, 8 relapsed and 3 showed clinical improvement. There were 14 cases of T. rubrum and a higher proportion of T. rubrum, 4 cases failed, 1 case with clinical cure. A further 2 out of 4 cases of T. tonsurans failed and all, that is, 2 of the T. violaceum relapsed (Table 7).

Our study concluded 14% relapsed from Ketoconazole against 28% for Griseofulvin. Legendre (5) reported 7% relapse rate in 14 patients at one month follow-up after 1–2 months of Ketoconazole.

Low relapse notes were also reported by Dageef (8) 5% in a 7-month follow-up, Jolly who had 9% relapse in 2 months of follow-up.

All the workers using Ketoconazole on recalcitrant cases reported relapsed rates between 30% to 75%. Robertson (9) in his follow-up for 5 months reported 30% relapse in T. rubrum. Cox (11) found a relapse rate of 36% in their patients followed for 1–14 months after 1–13 months courses of ketoconazole. Jones et al (10) had a 75% relapse rate at 5 months after Ketoconazole therapy of 3–10 weeks' duration. Whether in each case, prolonging therapy beyond the time of clinical and mycologic cure will affect the relapse rate, has yet to be determined.

Adverse effects had attracted much publicity in recent reports, especially on liver involvement. Previous experience has shown nausea (5%) to be the most frequent adverse reaction, with vomiting at (3%) and pruritis (1.5%). An analysis of 33 cases of hepatic injury associated with Ketoconazole therapy of an average of 56 days (10–219 days range), the biochemical pattern showed hepatocellular lesions in 50% of cases, and also intrahepatic cholestatic injury. Histological injury was rare and included focal to massive necrosis, or in centrilobular areas. No hepatotoxic metabolite has been identified to date (3, 12, 13, 14) Allergic reactions have not been reported so far. Our study shows only 2 patients complained of drowsiness and breathlessness.

Looking individually into the cases with relapse, the importance of host parasite/fungus relationship is shown to be of great importance. Other recent reports stress on the greater incidence of immune deficient hosts being affected with fungal infection (11).

Ketoconazole has shown, in our studies, to be very effective against dermatophyte. It provides a mycological cure in many patients who are recalcitrant cases and Griseofulvin resistant (8) non-inflamed T. rubrum cases.

It is a preferable first line choice in susceptible individuals eg immune deficient diseases, systemic lupus erythematosus, patients with malignancy; and being on steroids and cytotoxics.

Despite some of the reports on hepatic injury, Ketoconazole has good patient acceptance and few side effects.

Future studies of maintenance therapy with reduced intermittent dosages may provide methods of preventive recurrence in susceptible individuals.

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