

## KETOCONAZOLE IN TINEA VERSICOLOR: IS TEN DAY THERAPY ADEQUATE?

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### SYNOPSIS

Ketoconazole, an oral imidazole, discovered in 1980 (1), is an efficient drug for persistent localised Tinea versicolor, and extensive Tinea versicolor, giving a result of 93% cure (2) with a 30 day regime. In an attempt to minimise the dosage and reduce cost, a shorter course of 10 days at the dose of 200 mg per day was tried and found to be equally effective. We report 2 groups of patients, studied between November 1985 to December 1986. Group 1 consist of 20 patients and the aim was to find the minimal dosage to effect a mycological cure. The mycological cures were 25% at 10 days, a further 45% at 14 days and the rest, 30% by 20 days. However, when the patients were screened at the end of 28 days from the first dose, the final mycological cure was 80%. The extensive and chronic cases required longer treatment. Group 2 consist of 20 patients, who were treated with only 10 days of Ketoconazole, to find the low response at 10 days could be improved, and the cure rate at the end of 28 days did rise to 85%. Similar results were obtained with the 10 day dosage trials of the other investigators, which gave cures ranging from 78% to 100%. These results are equivalent to a cure with the 28 day regime. Moreover, the risk of possible side effects are reduced.

### INTRODUCTION

Tinea versicolor, a superficial fungus, caused by *Pityrosporum orbiculare*, has been treated with a large variety of topical preparations, from sodium thiosulphate (panau lotion) to imidazole creams but still remains a therapeutic problem, especially in the recurrent and extensive forms. Ketoconazole (1, 2, 3, 4, 5) an orally administered imidazole, provided a breakthrough in the last decade for cases of Tinea Versicolor. However, there is the reported side effect of possible liver dysfunction (6).

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The regime for Tinea Versicolor with Ketoconazole at 200mgm/day for 30 days was reduced to 10 days by several therapists in the attempt to reduce costs. They reported success rates ranging from 78% to 100%.

We studied its efficacy in cases of Tinea Versicolor in Middle Road hospital.

## METHODS AND MATERIAL

This study was carried out between November 1985 and March 1986. It is divided into two parts. The aims are:

1. To study the minimal dose to effect a mycological cure. This may be given in three dosages, 10 days, 14 days or 20 days at 200 mg (a tablet) per day.
2. To study the efficiency by giving only 10 days of Ketoconazole and noting whether the cure rate at 10 days could be improved on, when assessed at the end of the trial at 28 days.

### Group 1:

Twenty one patients were entered in the trial. One patient defaulted and twenty patients were assessed.

There were eighteen men and two women. All of them had Tinea versicolor, confirmed by mycological test (skin scrape) and examination and mapping its extent by the Wood's lamp. Those excluded from the trial include: children below 10 years of age, pregnant women, those with liver and renal disorders and anyone using anti-fungal therapy for the past week.

The data on patients, the duration of the disease, its recurrence, extent and sites of involvement, previous

treatment and any medical illness was recorded. Clinically, the symptoms and signs of itch and scaling and colour were noted.

The patients were assessed on day 0, Day 10, Day 14, day 28 for:-

- a) symptoms and signs of pruritis, scaling and erythema
- b) the extent of the lesions and its improvement and
- c) the test of cure, mycologically by fungal scraping, and by the Woods lamp, to see fluorescence of the fungus.

Ketoconazole, 200 mgm (each tablet) was taken daily, after food. No anti-fungal treatment was used. Patients were asked to report any side effect. A liver function test of hepatic transaminase, alkaline phosphatase, bilirubin and proteins was done.

### Group 2:

Another group of twenty patients were assessed in the same method as above except that only 10 tablets of Ketoconazole given as a fixed regime. The test of cure is assessed on Day 28 of the trial.

The following were taken as test of cure:

Cure: both the mycological test and Wood's lamp examination were negative.

Failure: if any of the above test is positive. This includes the partial cures, even if the residual involvement is minimal.

## RESULTS

### Group 1

Twenty patients, including 18 men and 2 women were studied. (Table 1) There were 12 Chinese, 4

TABLE 1  
GROUP 1: EPIDEMIOLOGY AND RESULTS

No:	Age (yrs)	Race	Sex	Duration (yrs)	Extent %	Site (of body)	Day-10 (extent % of rash)	RX-Days	Day-28	
1	41	Ch	M	0.25*	30	trunk, legs	leg	5	21	Fail
2	71	Ch	M	1	25	trunk	back	50	21	Fail
3	19	Mal	M	1	30	lower-body	abd	25	21	Fail
4	51	Ch	M	3	25	lower-body	leg	25	21	Cure
5	20	Ind	F	6	30	trunk	hip	5	21	Cure
6	36	Ind	M	3	60	whole body	leg	30	21	Cure
7	55	Ch	M	1	60	whole body & legs	back	30	14	Fail
8	24	Ch	M	3	20	trunk	trunk	100	14	Cure
9	19	Ch	M	4	50	trunk	trunk	100	14	Cure
10	52	Ch	M	0.5	60	whole-body	trunk	5	14	Cure
11	26	Ch	M	1	20	chest	thigh	5	14	Cure
12	51	Ch	M	0.5	80	whole-body	thigh	10	14	Cure
13	27	Ch	M	0.75*	45	whole-body	arm	5	14	Cure
14	18	Ch	M	0.16*	30	trunk, leg	chest	5	14	Cure
15	20	Mal	M	0.16*	20	trunk	chest	5	14	Cure
16	14	Ind	M	0.25*	30	trunk	—	—	20	Cure
17	17	Mal	F	3	30	trunk	—	—	10	Cure
18	38	Ind	M	1	10	trunk	—	—	10	Cure
19	18	Mal	M	0.5	15	trunk	—	—	10	Cure
20	12	Ch	M	0.2	10	legs	—	—	10	Cure

\*: recurrence

Malays and 4 Indians. The age range was 12—71 years, with 10 patients (50%) below 30 years, five (25%) between 30 and 50 years of age and five (25%) above 50 years.

The duration of their fungal disease ranged from one month to six years. Fourteen patients (70%) had the disease for less than 1 year, of these, four had recurrences. The extent in fourteen patients (65%) was more than 25% while 5 patients (20%) had 50% to 80% involvement. The sites were on the chest, back and upper limbs in 17 cases (85%) and on the legs in 3 (15%) patients.

Five patients (25%) were treated for 10 days, 9 patients (45%) were treated for 14 days and 6 patients (30%) for 20 days.

At Day 10, the mycological cure was low at 20%, ie in 5 cases. This increased at Day 28 to 80%, in 16 patients. The fungal scraping from the 4 failures showed isolated fragmented hyphae. Clinically, most of them had 80 to 95% clearance with parts of their leg, trunk or abdomen affected. Most were elderly and the duration of the infection was one year.

Thirteen patients (65%) had relief of itch by 10 days. Their itch had been present for many months. 3 of these had moderately severe pruritis. This is significant relief of symptoms and was commented on by patients. Seven patients (35%) improved, and the remaining 5 (25%) cleared by 28 days.

Three elderly men were markedly relieved of their itch, though this finally disappeared at 28 days

because their pruritis had caused them to develop prurigo papules and lichenified skin.

One patient, No: 4 had an elevated serum glutamic transaminase of 105  $\mu$ /l before the trial. There was no pathology found except that he was drinking 3 bottles of beer a night.

#### Group 2

Twenty patients, 17 men and 3 women were given 10 days of Ketoconazole. (Table 2) Their age ranged from 12 to 79 years. There were 11 Chinese, 7 Malays and 2 Indians. The duration of the fungal infection ranged from one month to 10 years. 12 patients had the infection for less than a year while the remaining eight had the infection for 1 to 10 years. The extent ranged from 10 to 50%. Nine (45%) had an extent of 10 to 20% involvement, and 11 patients (55%) had less than 25% involvement. All except one had tinea on the trunk. Eight persons suffered recurrent episodes. Six patients previously used sodium thiosulphide and one, used Daktarin cream. Medical illnesses included diabetes in one patient and atopy in another.

At 10 days, six patients (30%) were cleared while the others had improved. By Day 28, this result improved to 85%. Even the failures only had 5 to 15% residual involvement. Both the itch and scaling showed 75% clearance at the 10th day compared to 50% in the first group.

Patient No: 5 had elevated liver enzymes, serum transaminase of 76  $\mu$ /l at the beginning of the trial.

TABLE 2  
GROUP 2: EPIDEMIOLOGY AND RESULTS

No	Age	Race	Sex	Duration (yrs)	Extent %	Site	Day-10	Day-28
1	19	Ch	M	4*	30	trunk	chest	Fail
2	31	Ch	M	5	30	trunk	flank	Cure
3	25	Mal	M	5	30	trunk	chest	Cure
4	47	Ch	M	3	15	trunk	thigh	Fail
5	40	Ch	F	2	25	trunk	buttock	Fail
6	21	Mal	F	1	15	trunk	shoulder	Cure
7	25	Mal	M	6*	30	trunk	chest	Cure
8	29	Ch	M	1*	30	4 limbs	leg	Cure
9	30	Mal	M	1*	10	trunk	back	Cure
10	79	Ch	M	1	20	trunk	arm	Cure
11	67	Mal	M	1*	15	trunk	shoulder	Cure
12	14	Ind	M	0.16*	25	trunk	shoulder	Cure
13	71	Ch	M	0.16*	30	trunk	back	Cure
14	28	Ch	M	0.16	25	trunk	—	Cure
15	28	Ch	M	0.16	30	trunk	—	Cure
16	17	Mal	F	3	30	trunk	—	Cure
17	38	Ind	M	1	10	trunk	—	Cure
18	18	Mal	M	0.5	15	trunk	—	Cure
19	45	Ch	M	10	10	trunk	—	Cure
20	12	Ch	M	0.8	10	legs	—	Cure

\* recurrences

## DISCUSSION

The study shows that:

- the treatment regime for *Tinea versicolor* can be reduced to 10 days of Ketoconazole with a success rate of 85%.
- there is no significant difference in the cure rate in patients who are treated with a 10 day regime or longer.

In both groups, a mycological cure of 20 to 25% at the end of 10 days can be improved to 80 to 85%. (Table 3) Many patient showed marked clinical improvement, within the week. Sacwakontha (7) similarly reports of a cure of 23% at Day 10 and improving to 78% to Day 30. Most of them had about less than 20% residual involvement as detected on the Wood's lamp.

Pruritis is improved by 50-75% within a week and this is an important aspect of treatment. (Table 4) No adverse effects were noted. Two patients who had elevated liver enzymes before the trial, are being investigated.

50% for 2 and 3 doses. Ketoconazole 200mg for a week gave 66.7% cure. (9). Jacobs PH (15) reported cure of 60 in 62 patients on single dose of 400mg, with low relapse rate.

Sampaio (10) and Hay (13) have been unable to show any significant difference in the high cure and low relapse rate of pityriasis versicolor with various lengths of Ketoconazole 200mg/day. At 6 weeks, Sampaio reported 100% for 10 day treatment and 97% for 20 day treatment. Hay reported 80% (9 out of 12 cases) for his 15 day therapy.

Other authors have tried treatment regimes with shorter lengths of treatment. Results are reported for Ketoconazole at 200mg for 7 days, 66.7% by Sampaio (9) and 85% by Meisal (12). (Table 6) Cases of *Tinea versicolor* may be controlled with 400 mg Ketoconazole for five days, the total dose being the same, 2 gm, or possibly 400mg Ketoconazole for three days. In cases with recurrences, prophylaxis at 400mg/month is recommended.

In conclusion, a 10 day treatment for *Tinea versicolor* is acceptable and ingvarying the dose, a further reduction in the length of treatment is expected.

TABLE 3  
RESULTS OF THE TREATMENT OF PITYRIASIS VERSICOLOR  
WITH KETOCONAZOLE

	Group 1: 10-20 days (n = 20)		Group 2: 10 days (n = 20)	
	Day 10	Day 28	Day 10	Day 28
Mycological cure	5 (20%)	16 (80%)	6 (30%)	17 (85%)
Woods lamp clearance	5 (20%)	18 (90%)	7 (35%)	19 (95%)

TABLE 4  
SYMPTOMS AND SIGNS IN PATIENTS WITH TINEA VERSICOLOR  
TREATED WITH KETOCONAZOLE

	Group 1: 10-20 days (n = 20)			Group 2: 10 days (n = 20)		
	Day 0	Day 10	Day 28	Day 0	Day 10	Day 28
Pruritis:	20	9 (45%)	1 (5%)	20	3 (15%)	0
Scaling:	20	13 (65%)	0	20	3 (15%)	0

The possible explanation for these results with a 10 day regime is related to the pharmacology of Ketoconazole. Ketoconazole is excreted to a considerable extent via the sebaceous glands (8) and accumulates in them during the 10 days of treatment like a depot. This slow release from the sebum, which can take several weeks, combined with the affinity of the drug for keratinocytes creates a sufficiently adequate level of the active substance on the stratum corneum, even after cessation of treatment.

Our results have compared favourably to that of Sampaio, 90.9%, 1983 (9) and 100%, 1985 (10) Sacwakontha's 78.10% (7) Meisal 94.7%, 1983, (11) and 95%, 1985 (12) Hay and Midgley 80% (13) and Joliffe 88.5% (14). (Table 5)

Borelli was the first to find Ketoconazole effective in low doses. However, Sampaio's earlier work shows that lower doses of Ketoconazole gave poor results. These were 29.6% for one dose 400mg/week, 40% and

TABLE 5  
10 DAY KETOCONAZOLE THERAPY FOR TINEA  
VERSICOLOR COMPARISON OF RESULTS

Author		No. of Patients	Percentage Cure
1. Sampaio (San Paulo)	1983 1985	20/22 32	90.9% 100%
2. Sacwakontha (Thailand)		50/72	78%
3. Meisal (Germany)	1984 1985	15/19 24/25	94.7% 95%
4. Joliffe (UK)	1985	146/165	88.5%
5. Giam (Singapore)	1986	17/20	85%

TABLE 6  
TRIALS WITH VARYING DOSES OF KETOCONAZOLE  
IN TINEA VERSICOLOR

1. 400mg per week, a single dose	(Sampaio)	29.6%
2. 400mg per week, 2 doses	(Sampaio)	40%
3. 400mg per week, 3 doses	(Sampaio)	50%
4. 400mg per week, a single dose	(Jacob PH)	60/62
5. 200mg per day, 7 days	(Sampaio)	66.7%
6. 200mg per day, 5 days	(Meisal)	90%

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