ORAL KETOCONAZOLE — A NEW TREATMENT FOR TINEA VERSICOLOR

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SYNOPSIS

Ketoconazole (Nizoral R41400 Janssen Pharmaceuticals) was given orally at a dose of 200 mg to treat 90 patients with extensive or frequently recurring Tinea Versicolor. They received a total of 28 days of medication and 93% were cured after 4 weeks. At the end of a 3 month follow-up, of these 8 had relapsed (9%). Side-effects were minimal, only 5 patients suffered from pruritis, dizziness, chest discomfort, malaise and loss of appetite. No residual discoloration was noted in 22% of the patients at the end of 3 months. These results indicate that Ketoconazole is effective in the treatment of extensive Tinea Versicolor.

INTRODUCTION

Tinea Versicolor is a common tropical superficial fungal disease. It accounts for the sixth commonest dermatosis in hot and humid Singapore, in 1981. The fungus Pityrosporum orbiculare or Malassezia furfur is a lipophilic yeast fungus and has similar features with Pityrosporum ovale, a causative agent in seborrhoeic dermatitis. The knowledge of the etiology and pathogenesis has advanced greatly. It is known that under the influence of predisposing factors, e.g. genetic factors, hyperhidrosis, use of corticosteroids, defects in lymphokine production, defective T-cell function; the fungus changes from its saprophytic yeast form to its pathogenic mycelial form, very similar to the pathogenesis in Candida (1): The seborrhoeic sites of the trunk, neck, shoulders, thighs are frequently involved. These small scaly macules, mainly hypopigmented, becomes widespread and confluent. Besides this cosmetic disability, many patients complained of itch.

Ketoconazole was used to assess the response of this fungal infection. This is a new broad spectrum anti-fungal imidazole with a minimum of side effects. It is of interest that an oral agent is now available for this relatively benign but persistent skin infection.

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MATERIALS AND METHOD

90 Patients with extensive and recurrent Tinea Versicolor were selected for study. Age and sex distribution, duration of their infection, previous therapy, associated medical illnesses were studied.

The criteria for disease included a typical clinical picture of macules with fine scaling, positive yellow fluorescence with Wood's lamp and positive mycological identification of Malassezia Furfur with potassium hydroxide.

From this trial, Wood's lamp accurately mapped the extent of the infection, which was often more extensive than the naked eye could see.

Ketoconazole was given at a dose of 200 mg/day before food, for 28 days. Patients were assessed every fortnight for 2 months, then a further visit, 1 month later.

RESULTS

Clinical Data:

Age-Sex-Race distribution:

There were 71 males and 19 females, the males outnumber females by the ratio of four to one. Their ages ranged from 14 to 62 years with an average of 30 years. Most of them were in the economically gainful age (Table 1). The majority were Chinese, 60 persons (66%); with 12 Indians (14%), and 15 Malays (17%), and 3 Eurasians (3%).

The duration of Tinea Versicolor ranged from few months to 12 years, averaging 2.2 years. 58 patients (64%) were affected for less than 1 year. 4 of them (4%) had chronic Tinea Versicolor for 10–15 years. At least 47 patients (52%) had tried topical therapy. The majority 22 patients (24.5%) tried Sodium Thiosulphate and found it not very effective. 21 patients did not know the name of the creams prescribed by their doctors. The rest used Selsun (7 patients), Sulphur powder (4 of them), Panau Salap, a Chinese medication for fungus (3), Whitfield ointment (2), Steroid creams (2 patients). (Table 2)

Of the 20 patients, 7 had eczemas. The other illnesses include 1 of diabetes mellitus, 1 of Discoid Lupus Erythematosus, 1 of gastritis. 6 patients had concomitant skin infections, with 1 of folliculitis, 2 of viral warts, 1 of aspergilosus, 1 of trichomycosis and 1 of Tinea cruris, 4 of Acne vulgaris. (Table 3)

The skin lesions were extensive and confluent in 8% of patients, covering 70–90% of their body. 60% of them had confluent macular lesions over the seborrhoeic area of the trunk, covering 40–60%. The remaining 32% had a localised extent of up to 20% — 40% (Table 4).

The lesions were hypopigmented in 64 patients (71%), mixed with brown in 24 patients (27%), black in 1 patient and red in 1 patient.

80 patients or (89%) complained of pruritis on sweating. In the humid and hot climate, 51 patients (56%) found the itch at times intolerable.

Results of Therapy:

At the end of 4 weeks medication, 84 patients (93%) were cleared. The remaining 6 cases (7%) were treated with a further 2 weeks of Ketoconazole and cleared.

As for the symptoms pruritis improved rapidly, 89%

TABLE 1
AGE DISTRIBUTION

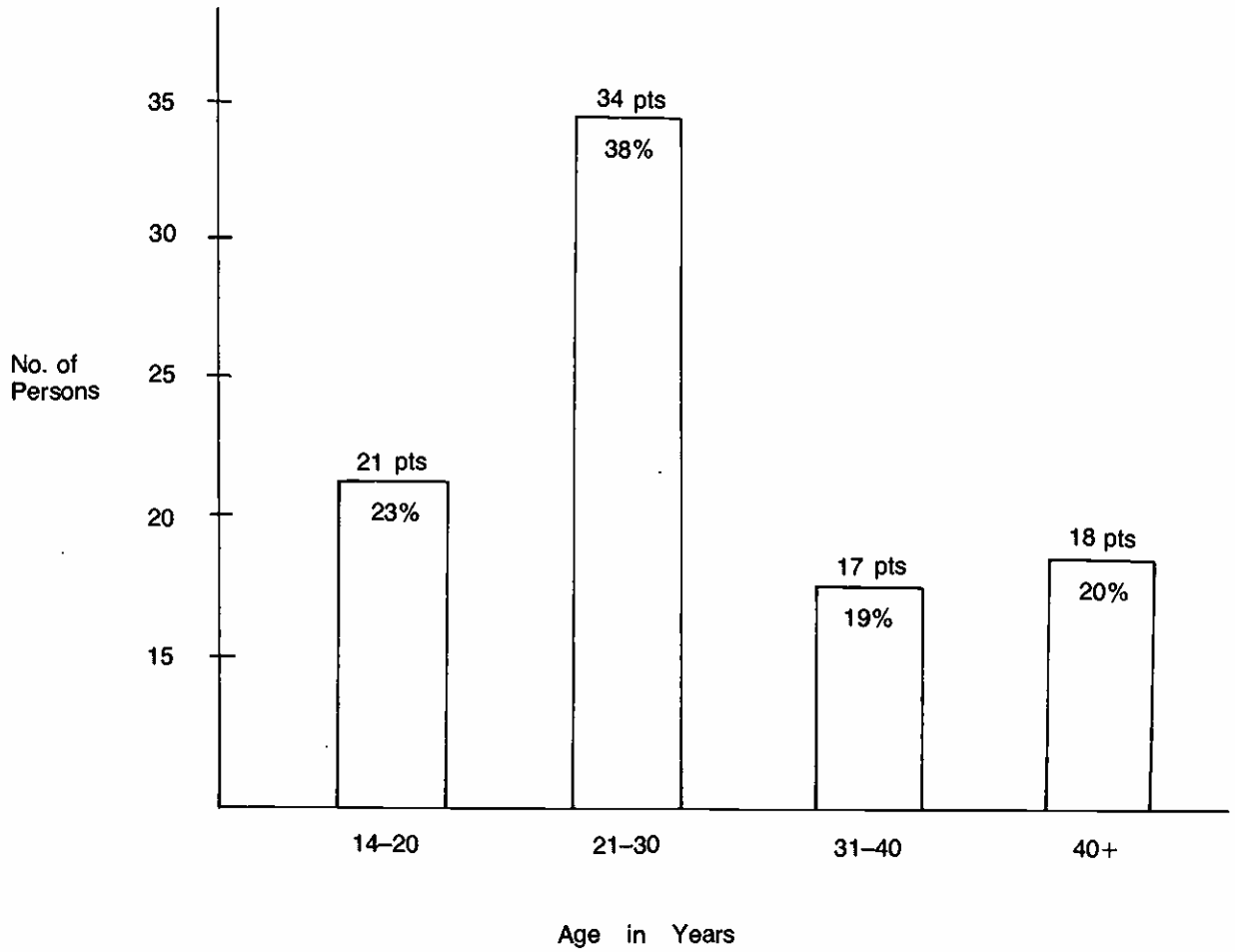
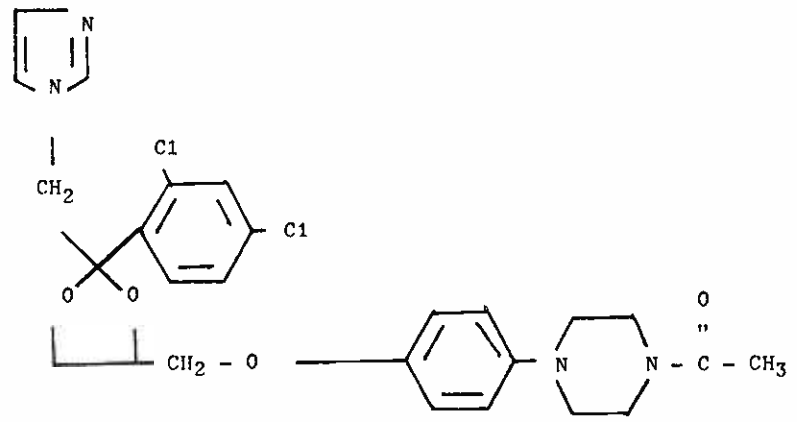


Fig. 1 - Chemical structure of Ketoconazole



Cis-1-acetyl-4(4-((2-(2-(2,-4-dichlorophenyl)-2-(1-H-imidazol-1-yl methyl) -1,3,-dioxolan-4-yl/ methyl) phenyl) piperazine

TABLE 2
TOPICAL THERAPY USED BY 47 PATIENTS

	Agent	No. of Patients
1	Sodium Thiosulphate	22
2	Creams	21
3	Selsun	7
4	Sulphur powder	4
5	Panau Salap	3
6	Whitfield ointment	2
7	Lime	1
8	Steroid cream	2

TABLE 3
MEDICAL ILLNESSES IN 2° PATIENTS

	Medical Illness	No. of Patients
1	Eczema	7
2	Diabetes Mellitus	1
3	Discoid Lupus Erythematosus	1
4	Gastritis	1
5	Infections (Folliculitis, Viral warts, Aspergillosus trichomycosis, Tinea cruris)	6
6	Acne vulgaris	4

TABLE 4
EXTENT OF LESIONS

Extent of Involvement	No. of Patients
70 – 90%	7
40 – 60%	54
20 – 40%	29

patients were asymptomatic by 4 weeks. The scaling cleared much slower with only 71% patients cleared at 4 weeks.

At the end of 3 months follow-up, 8 patients relapsed, giving a relapse rate of 9%. I was reinfected at 8 weeks, the rest at 12 weeks (Table 5). These included 2 females and 6 males of who 5 males were in the Army. Most of them had at least 36% involvement of the trunk and one had atopic dermatitis. All the Army boys complained of being unable to bath during the jungle training and of exercise sweating, possible predisposing causes. Both the females had recurrent chronic infection of 5 and 10 years each.

Side effects were minimal. 5.5% of patients had pruritis, chest discomfort, giddiness, malaise and loss of appetite. None had jaundice or hepatitis. Biochemical tests were not performed.

TABLE 5
TREATMENT WITH KETOCONAZOLE

Duration	Cured	%	Not Cured	Relapse
2 weeks	**61**	**67.5**	**29**	**—**
4 weeks	**84**	**93**	**6**	**—**
6 weeks	**90**	**100**	**0**	**—**
8 weeks	**89**	**99**	**—**	**1 (1%)**
12 weeks	**82**	**92**	**—**	**7 (8%)**
Conclusion	**82**	**92**	**—**	**8 (9%)**

DISCUSSION

Ketoconazole is a new imidazole antifungal drug. It is structurally related to the previous imidazoles (Fig 1), e.g. Miconazole but has a broad spectrum activity against superficial and deep fungal infections. The mechanism of action is probably related to disturbances in sterol or fatty

acid metabolism, or to effects on oxidative and peroxidative systems leading to accumulation of toxic endoperoxidases in the cell. Ketoconazole is well absorbed and is excreted in urine, saliva, and cerumen. It is well tolerated generally with minimal side effects. These reported side effects include gastrointestinal reactions (5%), pruritis (2%). Others are dizziness, somnolence, arthralgia, myalgia, headache. Gynaecomastia has been reported to occur in few male patients. In 10% of patients, elevated liver enzymes was detected with symptomatic liver dysfunction (2, 3). However, 20 cases of hepatitis were reported todate and one would use this with caution especially in children.

Todate, a number of trials have been held in multicentres internationally. Some of these investigations include Borelli (4) and Joliffe and Ngai (5) Faergemann (6) and Ford (7). Borelli studied 82 patients while Joliffe and Ngai studied 44 patients in 2 centres, but only Joliffe give 4 weeks therapy and followed them for 70 days. Heel (8) has also collected together the data from all preceding trials and analysed the overall results of 223 patients in multicentres.

In our study, most of the patients had rather extensive lesions. This selection was similar to Borelli's study (4). The fact that 60% of our patients had some treatment compared to 37% in Heel's data, suggests also that the topical therapy is ineffective. Our results show that at the end of the treatment, 4 weeks, 93% (64 cases) were cleared; the remaining 6 cases improved later. This correlates with Heel's data (Table 6). In Borelli's study, 95% were cured but three of them took only 1 or 2 tables. 82% of Faergemann's patients cleared with 3 weeks medication.

At the end of 3 months of our study only 82 patients were mycologically free i.e. 93% cured compared to Heel's 94%, Borelli's 93% and Faergemann's 93.4%. We had similarly noticed a rapid improvement of pruritis, compared to scaling. This is a useful clinical clue to assess improvement.

Like Candidiasis, endogenous factors plays a part in the pathogenesis of Tinea Versicolor. This is most likely related to the host defence systems. Thus, in such susceptible persons, relapses would be an unavoidable recurrence. Faergemann found a recurrence rate of 60% after 1 year and 80% after 2 years. Proposed prophylaxis with Ketoconazole 200 mg om has been tried in some studies (7) since predisposing factors cannot be eradicated. However, for the present in Singapore, Ketoconazole has proved to be effective in clearing the symptoms and extensive lesions where messy topical applications would not be effective. An oral tablet is very time saving, convenient and greatly increase the compliance of our patients.

TABLE 6
COMPARISON OF VARIOUS STUDIES

	Borelli 1980	Joliffe 1981	Faefgemann, Djary	Heel 1982	Rajan 1982
Patients	82	24	32 (double blind) 15 placebo	223	90
Cure at 4 weeks	95%	100%	82% (at 3 weeks)	92.4%	93%
Relapse: Duration of follow-up	7% (at 3–4 mths)	30% (2½ mths)	6.6% (3–7 mths) 1 had prophylactic Ketoconazole	7.6% (not stated)	9% (3 mths)

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