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Original Article

Open comparative study of efficacy and safety of ketoconazole soap and oral ketoconazole in tinea versicolor

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Abstract

Objective To compare the efficacy and safety of 2% ketoconazole soap in treatment of tinea versicolor (TV) and to compare it with stat 400mg dose of ketoconazole.

Methods Patients of TV confirmed by potassium hydroxide (KOH) mount were divided by block randomization into 2 groups. Group 1 received 400mg of oral ketoconazole single dose and a non-medicated soap for daily bath. Group 2 received 2% ketoconazole soap for daily bath. The lather from the soap while bathing was to be left on the skin for 3 minutes. Patients were assessed at the end one month and KOH repeated from index lesion.

Results Twelve patients out of 25 completed the study, 6 in each group. Four patients (66%) were mycologically cured in group 1 while two patients (34%) were mycologically cured in group 2. All these patients were compliant with the usage of soap.

Conclusion Ketoconazole soap is at best an adjunct in the treatment of TV. It might however be useful in the prophylactic management of patients with chronic TV as bathing is almost a daily routine in most patients especially in tropics. Further studies are required in this aspect.

Key words
Pityriasis versicolor, ketoconazole soap, ketoconazole tablet.

Introduction

Pityriasis versicolor or tinea versicolor (TV) is a superficial, often chronic infection of the skin caused by Malassezia species which is characterized by the formation of hypopigmented, hyperpigmented and/or erythematous macules predominantly on the trunk and upper arms, although other body parts can be involved sometimes. The treatment consists of antifungals like ketoconazole, fluconazole, clotrimazole, salicylic acid etc. The choice of preparation is often dictated by the extent of the disease and any underlying comorbidity. In extensive disease, oral preparations are preferred whereas in limited disease topical preparations. The various topical formulations available in the treatment of TV include creams, solutions, lotions and gels. Recently anti-fungal soaps have also been introduced in the market. Ketoconazole is one of the commonest antifungal used in the management of TV.

The aim of the study was to compare the efficacy of 2% ketoconazole soap versus oral

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ketoconazole 400mg in the management of pityriasis versiscolor.

Methods

This was an open study and ethical clearance was obtained from the hospital ethical committee prior to commencement. Patients willing to give informed written consent were chosen. Patients less than 14 years, pregnant and lactating females, those with severe hepatic insufficiency or who had used antifungal treatment in the preceding month were excluded. The study was conducted over two months' period (May and June 2011). All patients with a clinical diagnosis of TV were selected and a potassium hydroxide (KOH) mount was done from an index lesion. Only patients in whom the scraping was positive were included in the study.

The subjects were divided by block randomization into two groups. In group 1, cases received oral ketoconazole 200mg 2 tablets stat and were advised daily bath with a standard non-medicated soap once a day for one month. In group 2, patients were treated with 2% ketoconazole soap only for one month. Patients were advised to use the soap for bathing and to leave the lather for 3 minutes before washing off with water.

At the end of one month study period, all were evaluated clinically and a repeat KOH mount was done from the index lesion. Those who had not come for follow-up were considered as drop-outs. A patient was considered as cured if the index lesion on KOH mount was negative for fungus. Patients who reported an increase in the number of lesions were also considered as treatment failures or 'not cured'. The person performing the KOH mount was blinded with regards to the randomization and treatment undertaken by the patient. Adverse effects if any were recorded.

Results

Twenty five patients were recruited for the study and were randomized into group 1 (13 patients) and group 2 (12 patients). Of the 25 patients only 12 patients, 6 in each group, completed the study (**Table 1**). The average age group of group 1 was 25.7+6.4 years and of group 2 was 27.3+14.9 years. The median duration of disease in-group 1 was 3.8 months with an inter Quartile range (1.8, 15) and group 2 was 1 month with an inter Quartile range (0.7, 22.5).

In group 1, four patients (66%) had resolution of lesions, whereas one (17%) had no change in lesions and one patient (17%) had considerable residual lesions. In group 2, resolution of lesions was noticed in 2 patients (34%), while 3 patients (50%) showed considerable residual lesions and one patient (17%) had no change (chi square test p=0.122).

Mycological cure was noticed in four patients (66%) in group 1 and two (34%) patients in group 2 (chi square test p=0.248).

No side effects were noticed in patients of both the groups. The non-responders to treatment in both groups suffered from diabetes.

Table 1 Comparative results group 1 (oral ketoconazole) and group 2 (ketoconazole soap).

	Group 1	*Group 2*
Enrolled	13	12
Drop outs	7	6
Successfully completed	6	6
Cured	4 (66%)	2 (34%)*
Not cured	2 (34%)	4 (66%)

*p=0.248

Discussion

Tinea versicolor is one of the commonest fungal infections seen in tropical countries like India. Though perennial, increased incidence is noted in the summer months in view of increased temperature and sweating which tend to promote the growth of *Malassezia*. The high incidence of TV in summer prompted us to conduct the study in the month of May and June at the peak summer season in this part of the country.

Various antifungals have been used in the management of TV with varying success rate. The success rate of clearance depends upon the preparation of antifungal, duration and dose of treatment. Ketoconazole is one of the common drugs used in the management of TV. Ketoconazole was first used in the treatment of TV in 1980.[1] It is available in various formulations making it one of the most preferred medications in treatment of TV. The various formulations of ketoconazole available are tablet, cream, lotion, and shampoo base. Ketoconazole soap has been introduced in the market and is considered as an adjuvant in the management of TV. In order to avoid any bias due to the drug, the efficacy of ketoconazole soap was compared with oral ketoconazole. Oral ketoconazole has been used in different doses and for varying duration in various studies. Ketoconazole in a single dose of 400mg is one of the preferred regimens in the treatment of TV.[2,3] Patients on oral ketoconazole were given a non-medicated soap to use for one month, so as to avoid any accidental use of any over the counter medicated soaps which could interfere with the study results especially ayurvedic or antifungal containing soaps.

The success rates of ketoconazole in the treatment of TV in varying studies are summarized in **Tables 3** and **4**.

The lower response rate in both groups could be due to the fact that the non-responders in either group were diabetics. Patients with diabetes may require a longer duration of treatment in view of the immunosuppression and predisposition to fungal infection. Even though the formulation of ketoconazole soap was 2%, subsequent to creating lather with water, there may be a significant reduction in the available concentration which may account for the lower cure in this group. The shorter contact time of 3 minutes of a diluted concentration of active ingredient may also account for the lower cure rate.

Single dose of ketoconazole is very popular in the management of TV in view of better compliance and economics. The cure rate of 66% with oral ketoconazole 400mg is also comparable with that of Sadeque *et al*..[3] who reported a cure rate of 70.1% with 400mg stat of ketoconazole. Another study with 400mg of ketoconazole by Fernandez-Nava reported a cure rate of 42%.[2] Other studies which have quoted a higher cure rate have utilized ketoconazole for a prolonged duration of treatment varying from 5 days to 4 weeks and with a higher cumulative dose.[4,5,6,7]

Most of the patients visiting a dermatologist tend to prefer a topical preparation in the management of their skin problem. The topical preparation may be the only modality preferred or as an adjuvant. The advantages of topical therapy are lack of systemic side effects and higher concentration of the active drug in the skin. In widespread lesions of TV it is difficult and not economical to apply creams and ointments. Shampoo bases of ketoconazole are especially helpful for application over large areas of involvement. However these are associated with irritant reactions.[8] This is especially true if used on dry skin and/or kept

Table 2 Comparison of various studies on efficacy of ketoconazole tablet

Study	*Year*	*Dose (mg)*	*Duration (days)*	*Number*	*Cure rate (%)*
Giam *et al.*[5]	1984	200	28	90	93
Kaur *et al.*[1]	1991	200 mg	10	30	96.6
Patel *et al.*[6]	1993	200	14-21	13	100
Sadeque *et al.*[3]	1995	400	1 stat	75	70.1
Fernandez-Nava *et al.*[2]	1997	400mg `	1 stat	60	42
		200	10	60	51
Jain *et al.*[4]	1999	200	5	20	85
Nagpal *et al.*[7]	2003	200	14	20	90
Present study	2011	400	1 stat	6	66

Table 3 Comparison of various studies on efficacy of topical ketoconazole therapies.

Study	*Year*	*Type of preparation*	*Duration of application*	*Number*	*Cure rate (%)*
Savin *et al.*[12]	1986	Cream (2%)	11-22	51	84
Patel *et al.*[6]	1993	Not mentioned (2%)	14-21 days	15	100
Balwada RP *et al.*[13]	1996	Cream (2%)	14 days	20	90
Lange *et al.*[9]	1998	Shampoo (2%)	1 day and 3 days (5 minute contact)	103 and 106	69 and 73
el Euch *et al.*[14]	1999	Foaming gel (2%)	30 days	48	87.5
Chopra *et al.*[15]	2000	Cream (2%)	14 days	25	88
Rathi *et al.*[8]	2003	Shampoo (2%)	3 days (10 minute contact)	27	90
Aggarwal *et al.*[10]	2003	Shampoo (2%)	Once a week for 3 weeks (5 minutes contact)	20	95
Nagpal *et al.*[16]	2003	Cream (2%)	14 days	20	80
Muzaffar *et al.*[11]	2008	Gel (2%)	5 days (5 minutes contact)	25	92
Present study	2011	Soap (2%)	30 days	6	34

for longer time. Studies which have quoted a lower contact time with ketoconazole have reported a cure rate between 69% and 95%.[8,9,10,11]

Daily bath is almost a norm in India. By incorporating medications in soaps, the compliance can be ensured. All patients in both the groups were compliant in the usage of soap for the entire duration of the study. Allergic or irritant reactions to soaps are minimal and there are no systemic adverse effects from usage of soaps. No side effects were noticed in any patients in both groups.

The main shortcoming of our study was the smaller number of patients and the high drop-out rate. This may be in view of the patients not coming either due to cure of the condition or in view of summer vacation during study period. This was designed as a study of two months duration with recruitment over a month and follow-up after a month. The other limitation was that patients were not followed up for recurrence.

The main advantage of the method of treatment was the compliance with all patients reporting daily use of soap (in both arms of the study).

Topical ketoconazole in soap formulation may be best considered as an adjunct to oral treatment in management of TV, in order to enhance the cure rates. Ketoconazole soap may also be considered in the prophylactic management of patients with chronic relapsing TV. Further studies with a larger group of individuals with a longer follow up period are recommended.

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