Pityriasis Versicolor: Therapeutic Efficacy of Various Regimes of Topical 2% Clotrimazole Cream, Oral Flucanazole and Ketoconazole

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ABSTRACT

Introduction: Pityriasis versicolar is chronic superficial fungal infection caused by the organism Malessizia furfur. Pityriasis versicolar can be treated by various regimes of clotrimazole, Flucanazole and Ketoconazole. The therapeutic efficacy of these three drugs has been compared less. The study is aimed to evaluate the therapeutic efficacy of various regimes of clotrimazole cream, oral fluconazole and ketoconazole in the treatment of pityriasis versicolor.

Material and methods: A total of 75 patients were included in the study and were divided into 5 groups with 15 patients each and treated with various regimes conisisting of topical clotrimazole cream, oral fluconazole and ketoconazole. The results were recorded after a period of one month and analysed.

Results: In the group treated with tropical clotrimazole cream for one month and fluconazole 400mg single dose the clinical cure was 86% on an average. In the second group treated with topical clotrimazole cream for one month and fluconazole 150mg weekly for a period of 4 weeks the average clinical cure was 73%. In the third group treated with tropical clotrimazole cream alone for one month the average clinical cure was 73%. In the fourth group treated with fluconazole 400mg single dose alone showed a clinical cure of 36% on an average. The fifth group ketoconazole 400mg single dose alone the average clinical cure was 32% only.

Conclusion: Fluconazole 400mg single dose with topical clotrimazole cream therapy for one month is the most effective regime followed by tropical clotrimazole cream clotrimazole and fluconazole 150mg weekly.

Keywords: Pityriasis Versicolor, Clotrimazole Cream, Oral Flucanazole, Ketoconazole

INTRODUCTION

Pityriasis versicolor is a cutaneous superficial fungal infection characterized by skin pigmentary changes due to colonization of stratum corneum by dermophilic lypophilic fungus in the normal flora of skin known as Malessezia furfur.[1,2] It is one of the most common disorders of pigmentation in the world.[3] Pityriasis versicolar is also known as tiniea versicolar and less commonly as dermato mycosis furfurraceus, achromia parasitica and tinea flava.[3] Though world wide in distribution it is more common in tropics because of high temperature and humidity. The age distribution of the disease is variable with majority of cases occurring during adolescence.[4] Hormonal changes or increase in sebum secretion may be the cause.[5] This disease is most prevalently seen in tropics with an incidents as high as 40% in these regions.[6] In temperate areas it is more common during summer months.[7,8]

Pityriasis versicolor is caused by pitrosporum ovale and pitrosporum orbiculare, normal lipophilic and lipid dependent human flora that transformed into myceliar phase as Malessezia furfur.[3] P.Orbiculare and P.Ovale are identical in macromorphology but the difference lies in micromorphology, p.orbiculare having a tendency to produce simple spherical buds on narrow base, while p.oval produces single oval to cylindrical buds on broadbase.[9]

Pityriasis versicolor is a constituent of normal flora in 90 to 100% of populations.[10,11] Pityriasis versicolor occurs when yeast converts to mycelial phase as result of certain predisposing factors. The development of Pityriasis versicolor may be related to altered immune response to the organism[12,13]

The predisposing factors influencing Pityriasis versicolor may be classified as exogenous and endogenous. The exogenous factors are heat and moisture, occlusion of skin by clothing. Occlusion leads to altered microbial flora and altered PH range.[3] In temperate climate endogenous factors account for the prevalence of the disease. The endogenous factors are seborrhoeic dermatitis, cushing's syndrome, immunosuppressive therapy, malnutrition and hyperhidrosis(flexural).[14,15]

Pityriasis versicolor is generally rare among children although cases are more commonly seen in tropical climates.[16] Facial involvement may be more common in children than in adult.[17,18] Pityriasis versicolor is uncommon in adult (old people).[19] This is due to reduction in sebum production with advancing age.

The present study aims at evaluating the therapeutic efficacy of various agents both topical and systemic in the treatment of pityriasis versicolor. These agents include oral flucanozole, ketoconazole and topical clotrimazole cream.

MATERIAL AND METHODS

The study was conducted in Dermatology department of Mahatma Gandhi Hospital/ Kakatiya Medical College, Warangal, over a period of 1 year. The permission of local research ethical committee was obtained. There were 75 patients in the study group. A detailed clinical history was taken with regard to age, sex, family history, occupation, cytotoxic and immuno suppressive therapy and history of similar episodes in the path along with details of treatment for the same. Patients with hypopigmented lesion with following diagnostic criteria were selected for study. As the lesions were situated on private parts of the body like chest, young women who were not willing to under go examination were not taken into study. Children below 10 years, pregnant women and people with history of

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therapy for other disorders like malignancy and renal failure were excluded from the study. Patients who were already on treatment, and lactating woman were also excluded from the study.

The diagnosis of pityriasis versicolor was based on clinical features. The diagnostic criteria included hypopigmented or brown coloured macules which become augmented on scaping with a glass slide or blunt scalpel (Coup de ongle Beissner's sign). This was supported by bright yellow or gold coloured fluorescence under Wood's lamp examination.

The differential diagnosis includes vitiligo (particularly in dark skinned patients with hypopigmented lesion.), Cloasma, Tenia corporis, Seborrhoeic dermatitis, pityriasis rosea, pityriasis alba, erythrasma, pityriasis rotunda, secondary syphilis, confluent reticulate papillomatosis of Gougerot and Carteaud and pinta.

Whenever necessary skin scrapings were sent for mycological examination for detection of Malessizia furfur. All routine laboratory tests were done. Liver function tests were conducted in patients who were administered oral ketoconazole drug.

The patients were divided into 5 clinical groups each group consisting of 15 patients.

One group of patients were administered with single dose of flucanazole 400mg and were asked to apply tropical clotrimazole cream for a period of one month. *Second group* patients were given flucanozole 150mg weekly for a period of 4 weeks along with simultaneous topical therapy with clotrimazole cream for a period of 1 month. *Third group* patients were given topical therapy with clotrimazole cream alone for a period of one mont. *Fourth group* patients were administered with single starting dose of flucanozole 400mg only. *Fifth group* of patients were given single starting dose of 400mg of ketoconazole alone.

All the patients were followed up after a period of 7 days, 2 weeks, and one month and the results were recorded.

STATISTICAL ANALYSIS

Age and Sex incidence details, the site of the occurance of the lesions in patients in the study groups, the therapeutic efficacy of various regimes in the study groups were analyzed descriptively and tabulated with the help of Microsoft office 2007.

RESULTS

Majority of patients were young adults the youngest patient was 14 years old boy and the old age patient 45years old adult male (Table-1). The most commonly effected sites were chest – (Figure-1), neck, shoulders (Figure-2), upper arms (Figure-3) and face in order of frequency (Table-2). 80% of the patients had hypopigmented brownish yellow coloured macules. Rest of the patients had a combination of yellowish brown hypopigmented and dark brownish hyperpigmented macules. Majority patients were young adolescent and adult males. As the lesion were situated on chest, neck and shoulders, these parts being concerned with privacy of an individual most of the young females were not willing to be a part of the study group. Hence they were not included in the study. As a result no comment can be made on the sex ratio of affected individuals with Pityriasis versicolor.

Among 15 patients who were administered with flucanazole 400mg single dose along with topical application of clotrimazole cream for a period of 1 month. 5 patients reported with 100% clinical cure, 4 patients reported with 90% clinical cure, 5 patients reported with 80% clearance of the lesion and only 1 patient reported with 30% clinical cure. On an average there was 86 % clinical cure in this group (Table-3).

Within the group of 15 patients who were given flucanazole 150mg weekly for 4 weeks along with topical therapy of clotrimazole cream for a period of 1 month, 4 patients reported with 100 % clinical cure, 3 patients reported with 70 and 5 patients reported with 80% clearance of the lesions while 3 patients reported with 30% clearance of the lesions. On the whole the average clinical cure among this group is 73% (Table-4).

Age	Male	Female	Total
10 - 20	35	5	40
21 - 30	20	3	23
31 - 40	8	2	10
41 - 50	2	0	2
51 - 60	0	0	0
Total	65	10	75

Table-1: Age and sex incidence

Sl no	Site of Lesion	No.of Patients	Percentage
1	chest	40	53.4
2	Neck	12	16
3	Shoulders	10	13.4
4	Upper arm	8	10.6
5	Face	5	6.6
Total		75	100

Table–2: Site and frequency of lesion

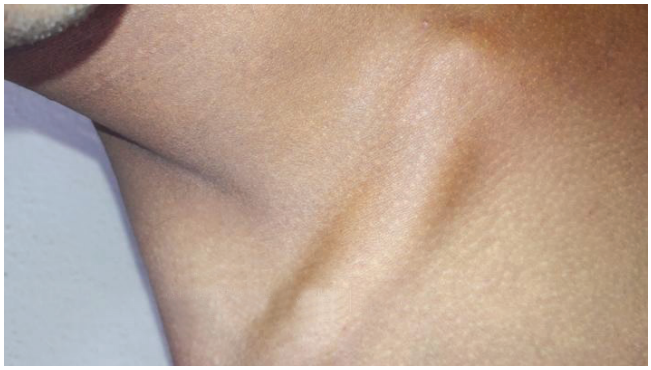

Figure-1: Patient with pityriasis versicolor lesions on chest

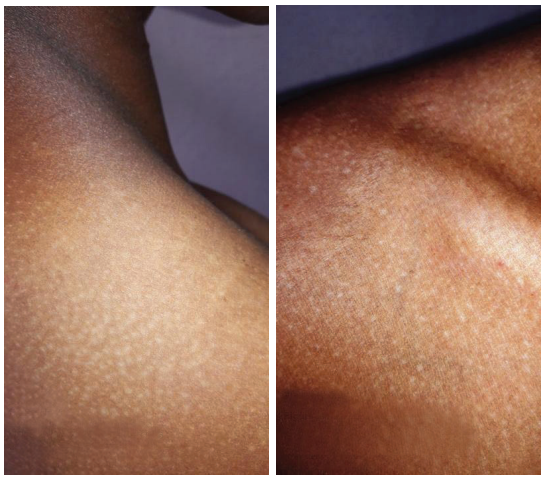

Figure-2: Patient with pityriasis versicolor lesions on shoulder; **Figure-3:** Patient with pityriasis versicolor lesions on upper arm

In the group of 15 patients who were treated with topical therapy of clotrimazole cream alone for a period of one month. 4 patients reported with 100% clinical cure, 3 patients reported with 70 and 3 patients reported with 80% clearance of the lesions while 5 patients reported with 50% clinical cure. There is an average clinical cure of 73% in this group (Table-5).

The other group of 15 patients who have received single starting dose of flucanozole 400 mg only, 3 patients reported with 70% clinical cure, 3 patients reported with 50% clearance of the lesions, 5 patients reported with 30% clinical cure while remaining 4 patients displayed only 10% clearance of the lesions. On the whole there is an average clinical cure of 36% in this group (Table-6), (Figure-4).

The last group of 15 patients who were administered with single dose of ketoconazole 400mg alone, 3 patients reported with 60% clearance of the lesions, 3 patients reported with 50% clinical cure, 3 patients reported with 30% clearance of the lesion while remaining 6 patients reported with only 10% clinical cure.(Figures-5 and 6). There is an average clinical cure of 32% in this group (Table-7).

DISCUSSION

Varied number of therapeutic options are available for the treatment of pityriasis versicolor. The anti fungal medications used are both topical and systemic. Topical therapy is the preferred mode in children as it is less expensive.[20] Low compliance due to reasons like odour and difficulty in applying over the back have led to the advent of oral medications like Fluconazole and ketoconazole which has got a clearance rate of as high as 97%[21] for the treatment of pityriasis versicolar. Systemic therapy is preferred in patients with extensive disease, frequent relapses and in whom topical drugs therapy have proved ineffective.[22]

The present study aims at the evaluation of various commonly

Sl no	Patients	Clearance rate at the end of one month
1	M 20	100
2	M 20	100
3	M 18	100
4	M 17	100
5	M 20	100
6	M 22	90
7	F 26	90
8	F 17	90
9	M 20	90
10	M 30	80
11	M 36	80
12	M 35	80
13	M 22	80
14	M 23	80
15	M 45	30

M-Male, F- Female; Average clinical cure = Percentage of total sum of clearance of all patients / No. of total patients in the concerned regime of therapy

Table-3: Clotramazole cream and Single dose Flucanazole 400mg

sl no	Patients	clearance rate at the end of one month
1	M 17	100
2	M 16	100
3	M 22	100
4	M 25	100
5	M 20	80
6	M 19	80
7	M 25	80
8	M 22	80
9	M 19	80
10	M 20	70
11	M 16	70
12	M 20	70
13	M 28	30
14	M 32	30
15	M 30	30

M-Male, F- Female; Average clinical cure = Percentage of total sum of clearance of all patients / No. of total patients in the concerned regime of therapy

Table-4: Clotramazole cream and Flucanazole 150mg weekly for 4 weeks

sl no	Patients	clearance rate at the end of one month
1	M 17	100
2	F 22	100
3	M 21	100
4	M 32	100
5	M 22	70
6	M 20	70
7	M 26	70
8	F 20	80
9	F 32	80
10	M 18	80
11	M 31	50
12	M 16	50
13	M 42	50
14	M 17	50
15	M 34	50

M-Male, F- Female; Average clinical cure = Percentage of total sum of clearance of all patients / No. of total patients in the concerned regime of therapy

Table-5: Clotramazole cream therapy alone for one month

Sl no	Patients	clearance rate at the end of One month
1	M 18	70
2	M 22	70
3	M 17	70
4	F 21	50
5	M 19	50
6	F 33	50
7	M 20	30
8	M 21	30
9	F 20	30
10	M 22	30
11	M 20	30
12	M 21	10
13	M 16	10
14	M 14	10
15	M 19	10

M-Male, F- Female; Average clinical cure 36 %; Average clinical cure = Percentage of total sum of clearance of all patients / No. of total patients in the concerned regime of therapy

Table-6: Flucanazole oral 400mg single dose

sl no	Patients	clearance rate at the end of one month
1	M 20	60
2	M 22	60
3	F 18	60
4	M 16	50
5	M 32	50
6	M 17	50
7	M 21	30
8	M 19	30
9	M 18	30
10	F 20	10
11	M 31	10
12	M 18	10
13	M 21	10
14	M 17	10
15	M 18	10
M-Male, F- Female; Average clinical cure 32 %; Average clinical cure = Percentage of total sum of clearance of all patients / No. of total patients in the concerned regime of therapy		

Table-7: Oral Ketoconazole 400mg single dose

used therapeutic agent like clotrimazole cream, oral flucanazole and oral ketoconazole.

Clotromazole belongs to azole group of drugs. These have fungistatic effect inhibiting the biosynthesis of ergoserol and thus disrupting the formation of fungal cellwall. HIV patients with pityriasis versicolor respond to topical azole as well as ketoconazole.[23,24] Clotromazole is a broad spectrum immudazole reported to be effective against the pityriasis versicolar in both open[25,26] and controlled double blind trials.[27,28]

Flucanazole is a triazole. It has been investigated for its effective use in treatment of pityriasis versicolar. Various studies have suggested that flucanazole is an effective treatment option for therapy of pityriasis versicolar.

With ketoconazole, an imidazole, a number of regimes have been devised for therapy of pityriasis versicolor. The most common regime is 200mg per day for 10 days. In a recent study comparing this regime with a 400mg single dose of ketoconazole didnot show any significant difference in outcome.[29] Ketoconazole affects the metabolosim of many drugs by inhibiting mammalin cytochrome 450 in addition to fungal cytochrome 450.[3] There is risk of elevation of serum transaminases on long term ketoconazole therapy.[30]

Systemic ketoconazole hepatoxicity appears to be idiosyncratic, more commonly seen in women above 40 years of age and is unlikely in one week such as in case of pityriasis versicolar.[31]

In the present study the first group of patients who were administered single dose of 400 mg flucanazole along with topical therapy of clotramazole for one month 33% of the group patients showed 100% clinical cure, 33% reported with 80% clearance while 27% showed 90% clinical cure whereas only one patient (7%) reported with 30% clinical cure after a period of one month.

This is the most effective regime in the treatment of pityriasis versicolar in the present study with a clinical cure of 86%.

In the second group where the patients were given flucanazole 150mg per week for 4 weeks along with topical therapy with clotramazole cream for 1 month. 27% patient reported with 100% clinical cure, 20% patients reported with 70% clinical cure, 33% patient showed 80% clearance of the lesion while

Figure-4: A patient 15 days after therapy with oral flucanazole 400mg single dose

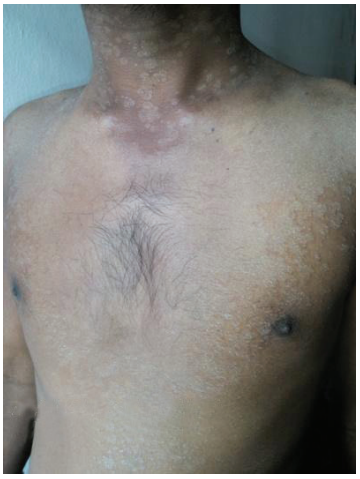

Figure-5: A patient 15 days after therapy with oral ketoconozole 400mg single dose

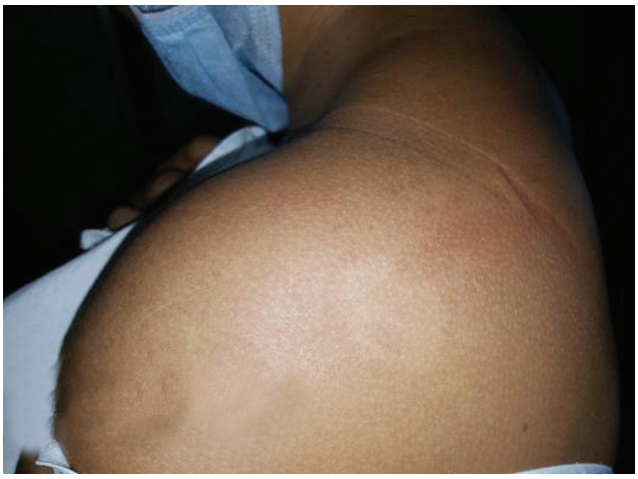

Figure-6: A patient after one month of therapy with ketocanozole 200mg single dose. only 10% of clearance of lesion

20% of patients showed 30% clinical cure. This regime with a clinical cure of 73% has got slightly lower efficacy than the above regime.

In another group of 15 patients who were treated with topical therapy with clotrimazole cream alone for a period of one month, 27% patients reported with 100% clearance of the lesions, 20% reported with 70% clinical cure, another 20% reported with 80% clinical cure while remaining 33% of patients in these group showed 50% clearance of lesions.

In the present study topical therapy with clotrimazole cream

alone also proved to be effective with a clinical cure of 73%.

In the fourth group of patients with administration of single dose of flucanazole 400mg 20% reported with 70% clinical cure, another 20% reported with 50% clearance of lesion while 33% showed 30% clinical cure and the remaining 27% of patients of this group reported with only 10% clinical cure. Thus clinical cure of this group is 36% on an average. Faergeman is his open controlled trial reported a clinical cure of 74% at the end of 3 weeks with single dose of 400mg flucanazole[32] but in the present study the average clinical cure rate is only 36%. Mantego Gel et al in their open control trial with single dose of 450mg flucanazole showed a mycological cure of 70% at the end of one month.[33]

In the last group of the patients who were given single dose of ketoconazole 400mg only 20% reported with 60% clinical cure, other 20% reported with 50% clearance of lesion, another 20% reported with 30% clinical cure while remaining 40% of this group reported with only 10% of clearance of lesions. Thus this group showed a clinical cure of 32% only at the end of one month of therapy. Fernandez Nova et al in there open control trial have shown mycological cure of 42% at the end of one month.[29]

In the present study single dose of 400mg of oral flucanazole along with topical clotrimazole cream for one month proved to be most effective therapy with a clinical cure 86%.

The drug flucanazole given as 400 mg single oral dose achieves high serum concentration and has got better fungistatic effect due to its longer half life. This effect of single dose oral flucanazole is potentiated by regular topical application clotrimazole cream leading to synergestic additive effect of both oral and topical therapy. Slightly lower results achieved by weekly oral flucanazole 150mg along with clotrimazole topical therapy for one month might be due to lower serum concentrations achieved by weekly dose of 150mg flucanazole which might have lead to lower fungistatic effect compared to single dose of flucanazole 400mg.

The fact that in the present study topical clotrimazole cream alone for one month has also achieved a clinical cure of 73% indicates that topical clotrimazole therapy plays a better role than a single dose or weekly dose of oral flucanazole and single dose therapy with ketaconazole as well.

In the present study single dose of oral flucanazole 400mg has achieved slightly better therapatic results than single dose of oral ketaconazole 400mg. In a study by Bhogal C.S. et al revealed that one oral dose of flucanazole 400mg might be better than one oral dose of 400mg ketoconazole.[34]

CONCLUSION

Fluconazole 400mg single dose with topical clotrimazole cream therapy for one month came out to be the most effective regime with 86% clinical cure followed by topical clotrimazole cream for one month and fluconazole 150mg weekly for a period of 4 weeks with a clinical cure of 73% and topical therapy with clotrimazole therapy for one month which had also achieved 73% clinical cure. Single dose of 400mg oral flucanazole with 36% clinical cure is better than single dose of oral 400mg ketoconazole which has got 32% clinical cure. Further studies on large scale are required in this regard.

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