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Original Research Paper

Dermatology

A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF TOPICAL ANTIFUNGAL AGENTS SERTACONAZOLE (2%) CREAM VERSUS KETOCONAZOLE(2%) VERSUS LULICONAZOLE (1%) CREAM IN PATIENTS WITH DERMATOPHYTOSIS IN A TERTIARY CARE CENTER AT KARAIKAL , PUDUCHERRY

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ABSTRACT

BACKGROUND: Sertaconazole is a new, broad spectrum, fungicidal and fungistatic imidazole with added antipruritic and anti-inflammatory activity that would provide greater symptomatic relief and hence would be beneficial in improving the quality of life for the patient with dermatophytosis.

AIM: To compare efficacy and safety of topical sertaconazole , ketoconazole and luliconazole in patients with dermatophytosis.

MATERIAL AND METHODS: 100 patients with tinea corporis and tinea cruris infections were enrolled in this single centre, randomized, open label parallel study. The initial 'Treatment Phase' involved three groups receiving either sertaconazole 2% cream applied topically twice daily for four weeks, ketoconazole 2% cream once daily for two weeks, luliconazole 1% cream once daily for two weeks. At the end of treatment phase, there was a 'Follow-up Phase' at end of 2 weeks, where the patients were assessed clinically and mycologically for relapse.

OBSERVATIONS: Out of 100 patients, 72 completed the study, sertaconazole (n = 24), ketoconazole (n = 26) and luliconazole (n = 22). The primary efficacy variables including change in pruritus, erythema, vesicle, desquamation and mycological cure were significantly improved in all the three groups, as compared to baseline, in the Treatment and Follow-up phase. Greater proportion of patients in sertaconazole group (85%) showed resolution of pruritus as compared to ketoconazole (54.6%); and luliconazole (70%), ($P < 0.05$ sertaconazole vs ketoconazole). There was a greater reduction in mean total composite score (pruritus, erythema, vesicle and desquamation) in sertaconazole group (96.7%) as compared to ketoconazole (92.6%) and luliconazole (91.9%). All groups showed equal negative mycological assessment without any relapses. All three study drugs were well tolerated.

CONCLUSION: Sertaconazole was better than ketoconazole and luliconazole in relieving signs and symptoms during study and follow up period. At the end of 'Treatment Phase' and 'Follow-up' Phase, all patients showed negative mycological assessment in all three treatment groups suggesting no recurrence of the disease.

KEYWORDS : Sertaconazole; Ketoconazole;luliconazole; Tinea Corporis/cruris;

INTRODUCTION:

Dermatophytosis is a common superficial fungal infection of the stratum corneum, hair and nails which contain keratin [1, 2]. The fungi causing dermatophytosis belongs to the genera Trichophyton, Microsporum and Epidermophyton [3, 4]. The specific causative agents of tinea corporis and tinea cruris most commonly are Trichophyton mentagrophytes, Trichophyton rubrum and Microsporum canis [5]. The prevalence of dermatophytosis is around 20-25% worldwide, and its incidence continues to rise [6]. However in India, the most commonly occurring clinical type of dermatophytoses for adults includes, tinea corporis (36-59%) and tinea cruris (12-27%).The dermatophytes remain as the only fungi to be dependent on human or animal hosts for their survival and dissemination [9].

Topical therapy is sufficient for the treatment of tinea infections however systemic agents are needed when the area of involvement is large or when there is secondary infection and also in immuno-compromised individuals[5]. At present, topical azoles and allylamines remain as the treatment of dermatophytosis. The main disadvantage with those agents is long duration of therapy, which results in poor compliance and a high rate of relapse.

The vast majority of antifungals are applied twice daily, although the newer ones introduced are applied only once daily. At present the research is focused towards shortening the frequency of application of antifungals and the duration of therapy in order to increase the patient compliance, to increase the cure rates and to decrease the relapse rates.

Imidazoles, allylamines and triazoles are most effective agents for dermatophytoses. Topical daily antifungal therapy usually involves imidazoles (namely, *Luliconazole*,*Ketoconazole* and *Sertaconazole*) .Luliconazole, an imidazole antifungal agent is active against dermatophytes and highly active against candida albicans but it inactive against zygomycetes. However treatment with antifungals has several clinical challenges including high relapse rates and recurrences that often occur after the discontinuation or stoppage of treatment. Also untreated and improperly treated infections may become chronic, causing significant disability and morbidity. To manage this growing pathogenicity of superficial fungal infections, development of newer broad spectrum antifungals like sertaconazole have opened up new treatment options.

Sertaconazole is a new benzothiophene imidazole derivative that is being used worldwide for varied indications including dermatophytosis, candidiasis, pityriasis versicolor, seborrhoeic dermatitis of scalp. Sertaconazole has both fungistatic and fungicidal activity against *Dermatophytes*, *Candida spp*. and *Cryptococcus* fungal infections. It is also

effective against *Aspergillus* fungi and Gram-positive bacteria (*Staphylococcus* and *Streptococcus genera*), that are likely to cause secondary infections.

Clinical efficacy and safety of these three topical antifungals has not been studied in Indian population and therefore the present study was undertaken to compare the efficacy and safety of sertaconazole 2% cream with ketoconazole 2% and luliconazole 1% for the treatment of superficial mycoses.

MATERIALS AND METHODS

Ethical clearance was obtained from the Institutional Ethical Review Board. A written informed consent was obtained from all the patients enrolled in the study.

INCLUSION CRITERIA:

1. Patients of either sex.
2. Age > 12 years of age.
3. Patients who are diagnosed with dermatophytosis.

EXCLUSION CRITERIA:

1. Immuno compromised individuals (H/o HIV infection, Diabetes mellitus, steroid intake).
2. Pregnant and lactating females.
3. H/o hypersensitivity reaction to azole antifungals.
4. Patients who received topical antifungal within 1 week before baseline visit.
5. Patients who received systemic antifungals within 4 weeks before baseline visit.

Patients fulfilling selection criteria were randomized to receive drugs as per randomization schedule in 1:1:1 ratio involving three study groups. Initial 'Treatment Phase' involved three groups receiving either sertaconazole 2% cream applied topically twice daily for four weeks, ketoconazole 2% cream once daily for two weeks, luliconazole 1% cream once daily for two weeks. At the end of treatment phase, there was a 'Follow-up Phase' at end of two weeks, where the patients were assessed clinically and mycologically for relapse.

Primary efficacy was based on clinical and mycologic assessment of *tinea lesion* at baseline, end of 'Treatment Phase ' and end of Follow-up Phase (2 weeks following completion of the treatment). *Clinical assessment* was based on the proportion of patients with symptoms and signs of *tinea lesions namely* pruritus, erythema, vesicle and desquamation, and graded as none (0), mild (1), moderate (2) and severe (3) depending on intensity. *Mycologic assessment* was based on KOH mounting for dermatophytes.

Secondary efficacy was a '*Composite Score*' of all clinical symptoms (*pruritus, erythema, vesicle and desquamation*); and '*Physician Global Assessment*' based on three criteria; successful treatment outcome (*clinical cure + negative mycology*), clinical success (*symptomatic relief + clinical cure*) and clinical failure (*no clinical and mycological improvement*), at end of 'Treatment Phase' and 'Follow-up Phase'.

Safety and tolerability was assessed by monitoring treatment related adverse events at each visit.

Patients who failed to follow up for two consecutive visits were considered as being lost to follow up and treated as drop outs.

STUDY DESIGN

It is a single-center, prospective, randomized, open-label, and comparative study. Patients with clinical evidence of tinea corporis/cruris attending Outpatient Department of Dermatology, Vinayaka missions medical college,karaikal.

STUDY DURATION

This study was conducted from June 2019 to June 2020.

STATISTICAL ANALYSIS

All randomized patients who received study medication and completed the study were included for analysis. The difference in change in clinical assessment of pruritus, erythema, vesicle and desquamation. Mycological assessment by scraping of skin scales and examination in 10% KOH mount and physician global assessment, within and between the groups were analyzed using Chi-square test. Baseline demographic data and laboratory investigations were analyzed using ANOVA.

RESULTS

Out of the 100 patients who were enrolled, 72 patients completed the study. In sertaconazole group, 8 patients were lost to follow up and 1 withdrew due to suspected contact dermatitis. In the Ketoconazole and luliconazole group, 8 and 11 patients were lost to follow up respectively. Baseline demographic data including age, weight and height in all the three treatment groups were comparable.

Primary efficacy results

Parameters	Sertaconazole	Ketoconazole	Luliconazole
No.of Patients	33	34	33
Male/Female	19/14	16/18	18/15
Age (yrs) (Mean + SD)	26.2 + 14.60	28.6 + 13.70	30.30 + 12.74
Weight (kg) (Mean + SD)	57.77 + 12.32	58.92 + 13.79	58.41 + 9.44
Height (cm) (Mean + SD)	160.34 + 8.25	161.87 + 9.20	161.99 + 7.65

Change in pruritus

At the end of treatment phase, the resolution of pruritus was seen in higher proportion of patients in sertaconazole group (87.5%) as compared to ketoconazole (61.5%); and luliconazole group (77.27%). The percentage of patients with change in pruritus was significantly more in sertaconazole group as compared to ketoconazole and luliconazole. During the 'Follow-up Phase', 100% of patients in sertaconazole and luliconazole group and 95.5% of the patients in ketoconazole group showed absence of pruritus.

Sertaconazole (n=24)

Severity	Baseline no.(%)	End of treatment no.(%)	Follow up no. (%)
None	-	21(87.5)	24(100)
Mild	3(12)	3(12.5)	-
Moderate	13(52)	-	-
Severe	9(36)	-	-

Ketoconazole (n=26)

Severity	Baseline no.(%)	End of treatment no.(%)	Follow up no. (%)
None	-	16(61.5)	26(100)
Mild	3(11.5)	9(34.60)	-
Moderate	14(53.8)	1(3.84)	-
Severe	9(34.6)	-	-

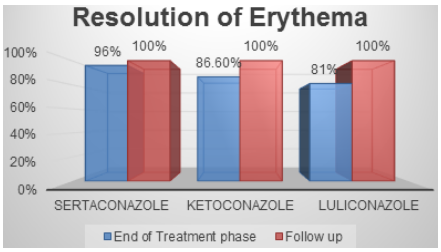
Luliconazole (n=22)

Severity	Baseline no.(%)	End of treatment no.(%)	Follow up no. (%)
None	-	17(77.27)	22(100)
Mild	2(9.0)	5(22.72)	-
Moderate	10(45.45)	-	-
Severe	10(45.45)	-	-

Change in erythema

At the end of treatment phase, the resolution of erythema was seen in higher proportion of patients in sertaconazole group

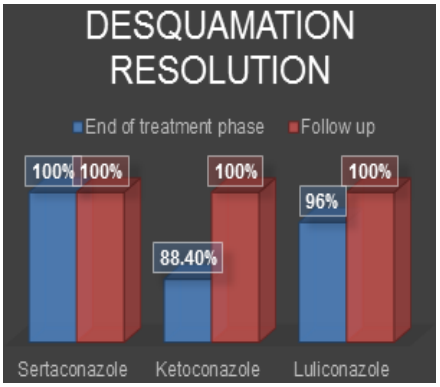
(96%) as compared to ketoconazole (86.6%); and luliconazole group (81%). During the 'Follow-up Phase', all the patients showed absence of erythema in all treatment groups.



Change in vesicle and desquamation

At baseline, 48% of patients had vesicles in all treatment groups. At end of 'Treatment Phase' and 'Follow-up' Phase, all patients showed absence of vesicles that was significant from the baseline.

At baseline, 70 to 100% of total study cases had desquamation in all treatment groups of which 52 to 74.2% of cases had moderate to severe desquamation. At the end of 'Treatment Phase', desquamation was absent in all patients in sertaconazole group (100%) as compared to ketoconazole (88.4%) and luliconazole group (96%). At the Follow-up' Phase, all patients showed absence of desquamation in all three groups.



Mycologic assessment

At baseline all patients had positive KOH test for Dermatophytes. At end of 'Treatment Phase' and 'Follow-up' Phase, all patients showed negative mycological assessment (negative KOH test).

Secondary efficacy results

Change in composite score

At baseline, the 'Composite Score' of all clinical symptoms and signs of *Tinea* infection (*pruritus, erythema, vesicle and desquamation*) was 6.44 in sertaconazole group, 6.52 in ketoconazole group and 7.25 in luliconazole group. At the end of 'Treatment Phase', there was a greater reduction in mean total composite score in sertaconazole group (96.8%) as compared to ketoconazole (91.2%) and luliconazole group (93.6%). At the end of 'Follow-up Phase', the mean total composite score was zero in sertaconazole and luliconazole group and 0.05 in Ketoconazole group.

Changes	Sertaconazole (n=24)	Ketoconazole (n=26)	Luliconazole (n=22)
Baseline	6.44+ 2.36	6.52+1.63	7.25+2.39
End of treatment	0.23+0.43	0.56+0.74	0.50+ 0.41
% Reduction	96.8	91.2	93.6

The improvement in the total composite score was well reflected clinically in patients with tinea corporis as shown in below images.

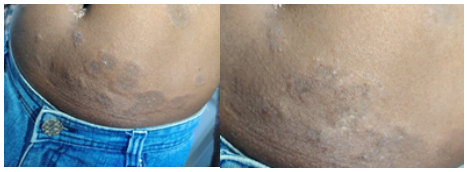


Image (a) : A patient on Ketoconazole – at the end of treatment phase.

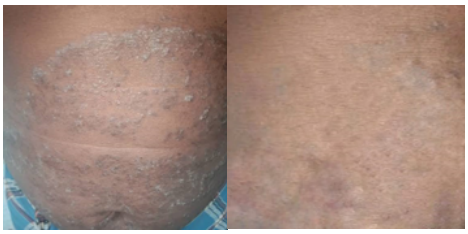


Image (b) : A patient on Sertaconazole – at the end of treatment phase.

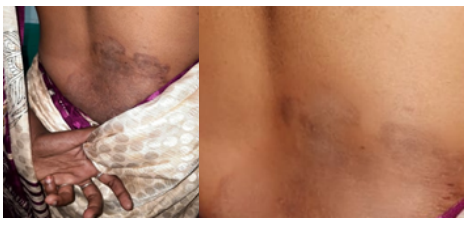
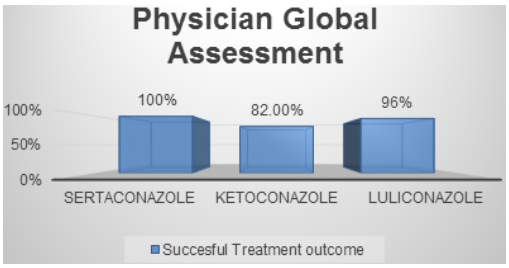


Image (C) : A patient on Luliconazole – at the end of treatment phase.

Physician global assessment

Physician Global Assessment at end of 'Treatment Phase', the 'Successful Treatment Outcome' was 100% in sertaconazole group as compared to ketoconazole (82%) and luliconazole (96%).



Safety Parameters

All three study drugs were well tolerated. Only one patient in sertaconazole group withdrew from the study due to suspected allergic contact dermatitis.

DISCUSSION

Dermatophytes are group of taxonomically related fungi that invade the keratinized tissue (skin, hair, and nails). The disease is most common in tropical countries like India. The incidence of tinea infections has progressively increased since the 1970s owing to increase in the population of immunocompromised individuals.Clotrimazole which belongs to azole group is the most commonly encountered broad-spectrum topical antifungal agent. Sertaconazole is a newer topical benzothiophene imidazole antifungal, found to be more effective than conventional azoles in several studies.

Dermatophytoses is one of the most earliest known fungal infections and affects the quality of life of patients due to the concomitant inflammatory symptoms involving pruritus. Recurrence of tinea infections is common due to inadequate treatment or reinfections especially of the intertriginous areas.

In the present analysis based on data of 72 evaluable patients, all the three study drugs showed significant reduction in signs and symptoms (*pruritus, erythema, vesicles* and *desquamation*) of tinea infections as compared to baseline. At end of 'Treatment Phase' greater proportion of patients in sertaconazole group had absence of pruritus (88%) and erythema (96%) as compared to ketoconazole and luliconazole.

This substantiates the antipruritic and anti-inflammatory action of sertaconazole over other antifungals that would ensure better adherence to treatment and improved quality of life. This antipruritic and anti-inflammatory property of sertaconazole is due to its ability to reduce histamine release and several other proinflammatory cytokines including PGE2. The clinical implication of this is significant since for most patients with tinea infections topical imidazoles are usually advocated where sertaconazole shows highest antimycotic potency compared to other antifungal agents especially against *candida albicans* that are also likely to be involved or concomitantly present in a patient of tinea cruris.

Significant improvement in vesiculation and desquamation was observed in all three groups compared to baseline.

At the end of 'Treatment Phase' and 'Follow-up' Phase, all patients showed negative mycological assessment in all three treatment groups, suggesting of no recurrence of the disease.

As per physician global assessment, all patients in Sertaconazole group (100%) had successful treatment outcome (clinical and mycological cure) as compared to ketoconazole (82%) and luliconazole (96%).

In the present study, all three treatments were well tolerated and found to be safe. One patient in the sertaconazole group had complained of burning sensation on application. This could be attributed to the pharmacological property of any topical antifungal drug or hypersensitivity to the study drug, that could not be assessed since the patient was lost to follow-up.[13]

There have been a several limitations in our study, e.g., (a) This was an open-label design, (b) smaller sample size, and (c) the diagnosis of tinea was based only on KOH mount but not on culture.

CONCLUSION

The results of the present study indicate that sertaconazole was better than ketoconazole and luliconazole in relieving signs and symptoms of dermatophytoses especially pruritus thereby improving patients' quality of life. The mycological cure was similar in all the three drugs at the end of treatment and follow up period. The mean percentage reduction in total composite score was 97.1%, 91.2% and 92.9% for sertaconazole, ketoconazole and luliconazole group respectively, suggesting comparable efficacy of the studied anti-fungal agents at the end of follow-up phase. Only one patient reported suspected contact dermatitis suggesting excellent safety and tolerability of sertaconazole, luliconazole and ketoconazole.

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