DOI: 10.7860/JCDR/2014/10210.4866

Original Article

Pharmacology Section

Comparison of Topical Anti-Fungal Agents Sertaconazole and Clotrimazole in the Treatment of Tinea Corporis-An Observational Study

RAGHU PRASADA MALLADAR SHIVAMURTHY[1], SHASHIKALA GOWDARA HANUMANTAPPA REDDY[2], RAVINDRA KALLAPPA[3], SHANKAR ACHAR SOMASHEKAR[4], DEEPA PATIL[5], UMAKANT N PATIL[6]

ABSTRACT

Objectives: To compare the efficacy of topical antifungal agents, Sertaconazole and Clotrimazole in Tinea corporis patients.

Materials and Methods: A total of 60(n=60) patients were included in the study. They were divided into two groups of 30 patients each. First group included patients treated with topical Sertaconazole as test drug whereas the second group constituted patients treated with topical Clotrimazole as standard drug. The patients were advised to apply the drug on affected area twice daily for three weeks. The parameters like erythema, scaling, itching, margins and size of the lesion and KOH mount were taken for the assessment of efficacy. This was an open labelled study and patients were followed up every week for three weeks.

Results: The total score included all grades in erythema, itching, scaling, margins and size of lesion and KOH mount. There was significant reduction in erythema ($p<0.02$) and highly significant reduction in scaling ($p<0.001$), itching ($p<0.001$) and margins of lesion ($p<0.001$) among Sertaconazole group. The mean difference and the standard deviation of total scores for Clotrimazole were 7.20 and 1.69 and for Sertaconazole group 8.80 and 1.52 respectively. The p-value on application of students unpaired t- test was $p<0.001$ (Highly significant).

Conclusion: From the present study, it can be concluded that topical Sertaconazole shows better improvement in the clinical parameters than topical Clotrimazole within a span of three weeks in the treatment of T corporis.

Keywords: Antifungal agents, Clotrimazole, Sertaconazole, Tinea corporis

INTRODUCTION

The incidence of topical fungal infections has progressively increased in recent years primarily because of an increased number of immunocompromised patients and the increased use of health clubs and community swimming pools, which favour the spread of infections [1,2]. Dermatophytes are group of taxonomically related fungi that invade the keratinized tissue (skin,hair,nails) of humans or other animals resulting in an infection called dermatophytosis [3]. Tinea corporis refers to all dermatophytosis of glabrous skin except the palms, soles and groin. This disease can be treated with topical and oral antifungal drugs. There are several topical antifungal agents like Fluconazole, Clotrimazole, Ciclopirox, Naftifine, and Terbinafine and so on [4]. Clotrimazole is broad spectrum topical antifungal agent. It is generally well tolerated but in some cases erythema, burning, stinging, peeling, blistering, oedema, pruritis and urticaria at site of application are reported. It is applied twice daily for three weeks for T corporis [5,6]. Sertaconazole is a newer topical imidazole found to be more active than other azole antifungals in several studies [7,8]. It is also reported that once daily application for three weeks regimen of Sertaconazole showed improved patient compliance which is important in successful treatment of dermatomycoses [7,8].

Hence, the present study was undertaken to study the antifungal efficacy of Sertaconazole and compare with the commonly used antifungal Clotrimazole in Tinea corporis.

OBJECTIVES OF THE STUDY

1) To compare the efficacy of topical antifungal agents, Sertaconazole and Clotrimazole in Tinea corporis patients.

MATERIALS AND METHODS

The present study on dermatophytosis was carried out after the Institutional Ethical Committee approval in the Department of Dermatology, J. J. M. Medical College and Chigateri General Hospital, Davangere, Karnataka, India, over a period of two years from Dec 2009 to Jan 2012. A total of 60(n=60) patients were included in the study. Written informed consent was taken from all the patients. The diagnosis and treatment of Tinea corporis was done with the help of consultant Dermatologist. They were divided into two groups of 30 patients each. The average age of clotrimazole and sertaconazole groups were 31.93 and 33.33 with standard deviation of 13.18 and 11.99 respectively, showing that their age group was much similar. After taking history, a detailed clinical examination of the patient was done in good light to determine the number of lesions, the types, presence of inflammatory margin and the extent of involvement. First group included patients treated with topical Sertaconazole cream as test drug whereas the second group constituted patients treated with topical Clotrimazole cream as standard drug. The patients were advised to apply the drug twice daily for three weeks. The parameters like erythema, scaling, itching, margins and size of the lesion and KOH mount were taken prior to treatment and at the end of three weeks. The study method was open label method.

Chemicals and drugs

a) Sertaconazole 2% cream used as the test drug was obtained from Torrent Company.

b) Clotrimazole 2% cream used as standard drug was obtained from government hospital. (Karnataka antibiotics and pharmaceuticals limited).

c) All the patients received tab Teczine (levocetrizine 5mg) once daily for 10 d.

d) Potassium hydroxide (KOH) mount of skin scrapings from the affected site was used for confirmation of clinical diagnosis [9].

Patient Inclusion Criteria

The patients were included from the age group of 15-60 y, having clinical manifestations of Tinea corporis such as erythema, scaling,

Erythema Grade	Clotrimazole group		Sertaconazole group	
	Pre treatment patients	Post treatment patients	Pre treatment patients	Post treatment patients
	No. (%)	No. (%)	No. (%)	No. (%)
0	0(0.0)	9(30.0)	0(0.0)	29(96.7)
1	10(33.3)	19(63.3)	0(0..0)	0(0.0)
2	15(50.0)	2(6.7)	30(100.0)	1(3.3)
3	5(16.7)	0(0.0)	0(0.0)	0(0.0)
Total	30(100)	30(100)	30(100)	30(100)

[Table/Fig-1]: Comparison of pre and post treatment erythema in Clotrimazole group and Sertaconazole group., **P< 0.001HS,** *Wilcoxon signed rank test*

Erythema Grade	Clotrimazole group		Sertaconazole group	
	Pre treatment patients	Post treatment patients	Pre treatment patients	Post treatment patients
	No. (%)	No. (%)	No. (%)	No. (%)
0	0(0.0)	9(30.0)	0(0.0)	17(56.7)
1	5(16.7)	20(66.7)	13(43.3)	13(43.30)
2	21(70.0)	1(3.3)	16(53.3)	0(0.0)
3	4(13.3)	0(0.0)	1(3.3)	0(0.0)
Total	30(100)	30(100)	30(100)	30(100)

[Table/Fig-2]: Comparison of pre and post treatment scaling in Clotrimazole group and Sertaconazole group

Itching Grade	Clotrimazole group		Sertaconazole group	
	Pre treatment patients	Post treatment patients	Pre treatment patients	Post treatment patients
	No. (%)	No. (%)	No. (%)	No. (%)
0	0(0.0)	9(30.0)	0(0.0)	23(76.7)
1	0(0.0)	20(66.7)	9(30.0)	7(23.30)
2	30(100.0)	1(3.3)	20(66.7)	0(0.0)
3	0(0.0)	0(0.0)	1(3.3)	0(0.0)
Total	30(100)	30(100)	30(100)	30(100)

[Table/Fig-3]: Comparison of pre and post treatment itching in Clotrimazole group and Sertaconazole group

Margins Grade	Clotrimazole group		Sertaconazole group	
	Pre treatment patients	Post treatment patients	Pre treatment patients	Post treatment patients
	No. (%)	No. (%)	No. (%)	No. (%)
0	0(0.0)	7(23.3)	0(0.0)	2(6.7)
1	0(0.0)	23(76.6)	1(3.3)	28(93.3)
2	30(100.0)	0(0.0)	0(0.0)	0(0.0)
3	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total	30(100)	30(100)	30(100)	30(100)

[Table/Fig-4]: Comparison of pre and post treatment margins in Clotrimazole group and Sertaconazole group., p<0.001 HS, *Wilcoxon signed rank test*

Size Grade	Clotrimazole group		Sertaconazole group	
	Pre treatment patients	Post treatment patients	Pre treatment patients	Post treatment patients
	No. (%)	No. (%)	No. (%)	No. (%)
0	2(6.7)	13(43.3)	0(0.0)	15(50.0)
1	10(33.3)	8(26.7)	20(66.7)	15(50.0)
2	14(46.7)	6(20.0)	9(30.0)	0(0.0)
3	4(13.3)	3(10.0)	1(3.3)	0(0.0)
Total	30(100)	30(100)	30(100)	30(100)

[Table/Fig-5]: Comparison of pre and post treatment size in Clotrimazole group and Sertaconazolegroup., p<0.001 HS, Wilcoxon signed rank test

KOH Grade	Clotrimazole group		Sertaconazole group	
	Pre treatment patients	Post treatment patients	Pre treatment patients	Post treatment patients
	No. (%)	No. (%)	No. (%)	No. (%)
0	0(0.0)	29(96.7)	0(0.0)	30(100.0)
1	0(0.0)	0(0.0)	0(0.0)	0(0.0)
2	30(100.0)	1(3.3)	30(100.0)	0(0.0)
3	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total	30(100)	30(100)	30(100.0)	30(100.0)

[Table/Fig-6]: Comparison of pre and post treatment KOH mounts investigation in Clotrimazole group and Sertaconazole group., P<0.001 HS, Wilcoxon signed rank test

Parameter	Range	Median	Range	Median	Median difference	p* value, sig
Erythema	1-3	2	1-3	2	0	0.2 NS
Scaling	1-3	2	1-3	2	0	0.06 NS
Itching	1-3	2	1-3	2	0	0.21 NS
Margins	1-3	2	1-3	2	0	0.31 NS
Size	0-3	2	0-3	1	1	0.07 NS
Koh Mount	0-2	2	0-2	2	0	1.0 NS

[Table/Fig-7]: Comparison of pre treatment values of both the Clotrimazole and Sertaconazole groups., *Mann Whitney U-test

Clotrimazole Group			Sertaconazole Group			p* value, sig
Parameter	Range	Median	Range	Median	Median difference	
Erythema	0-2	1	0-1	0	1	0.02 S
Scaling	0-2	1	0-1	0	1	0.001 S
Itching	0-1	1	0-1	0	1	<0.001 HS
Margins	0-1	1	0-1	0	1	<0.001 HS
Size	0-3	1	0-1	1	1	0.11 NS
Koh Mount	0-2	0	0-2	0	0	0.31 NS

[Table/Fig-8]: Comparison of post treatment values of both the Clotrimazole and Sertaconazole groups., *Mann Whitney U test

vesicles, pustules, itch, and skin scraping positive for KOH (Potassium hydroxide) mount.

Patients Exclusion Criteria: Patients with systemic mycosis or mycosis of the hands face and scalp, Oropharyngeal mycosis, vaginal mycosis, Pre-treatment with antifungal drugs and immunosuppressive agents within 14 and 30 d respectively, prior to the onset of study were excluded. Pregnancy, lactation or inadequate contraception in women of child bearing potential, participation in another study within 30 d prior to the commencement of the study, patients with history of hypersensitivity to azole drugs or vehicle ingredients, patients with history of diabetes mellitus, severe psychiatric illness and other systemic illness and Patients who are unwilling to give written consent were also excluded.

Efficacy parameters: The patients were monitored for the following signs.

Colour of the lesion [6]: Change in colour from erythema to normal skin colour was noted. The scoring was given in following manner: 0=absent, 1=mild, 2=moderate, 3=severe.

Scaling of the lesion [6]: The Scoring was given in the following manner: 0=Absent, 1=Mild, 2=Moderate, 3=Severe.

Itching [6]: The scoring was given in the following manner: 0=no itching, 1=Mild itching not affecting daily activities, 2=Moderate itching affecting daily activities, 3=Severe itching disturbing the sleep.

Margins of the lesion [6]: Whether the lesion shows progressive (presence of papules, vesicles) or regressive pattern (return to normal skin pattern). Scoring was given in following manner: 0=Regressive, 1=Stagnant, 2=Progressive.

Size of the lesion [6]: Whether there was increase or decrease in size. Scoring for lesion size was as follows: 0=size less than 5cms

Parameter	Mean difference		Post-treatment patients
	Clotrimazole Group	Serptaconazole Group	
Mean	7.20	8.80	p<0.001 HS
SD	1.69	1.52	

[Table/Fig-9]: Comparison of pre and post treatment total scores in Clotrimazole and Sertaconazole group., **Student's unpaired t test*

in circumference, 1=size 5-10cms, 2=size 10-20cms, 3=size > 20cms.

KOH mount [6]: The scoring was given as: 0=KOH negative, 2=KOH positive.

In the present study, the efficacy of the topical treatment is determined by shifting of patients from grade 3 to grade 2, grade 2 to grade 1, grade 1 to grade 0 with each parameter. Grade 0 is the highest level of cure that can be attained by any patient. So the primary aim of treatment was to bring the patient to grade 0. The total score includes the scores of colour of the lesion, scaling of the lesion, itching, margins of the lesion, size of the lesion and KOH mount.

STATISTICAL ANALYSIS

After collecting the raw data, the values in all the groups were analyzed by using Wilcoxon signed rank test, Mann Whitney test and students unpaired t-test.

DISCUSSION

The antifungal properties of Sertaconazole have been evaluated in a few in-vitro studies [10,11]. In one of these studies, isolates of T. Rubrum showed a higher sensitivity to Sertaconazole than to Bifonazole, Fluconazole And Cyclopyroxolamine but not to Amorolfine or Terbinafine [12]. In a comparative study of susceptibility against 250 clinical isolates of dermatophytes and Scopulariopsis Brevicaulis, Sertaconazole was shown to be one of the most effective among ten antifungal agents evaluated [13]. Sertaconazole showed a broad range of fungicidal activity in one study [14]. The pharmacokinetic data shows that, immediately following topical application of 100mg single dose 2% Sertaconazole cream on the skin of the back of 12 healthy volunteers, about 89% of the compound was recovered on the skin surface [15]. The clinical efficacy data shows that clinical cure rate and the mycological cure rate of 2% Sertaconazole cream twice daily was significantly greater than that of 2% miconazole cream twice daily in patients with a range of cutaneous mycoses [16]. In the present study we have compared Sertaconazole and Clotrimazole topical cream among two groups of patients with comparable age. Fungal infections of the dermis may elicit a local inflammatory response that results in irritation and itching. The anti-inflammatory properties of Sertaconazole have been evaluated in both in-vitro and in-vivo animal studies. In human peripheral blood lymphocytes stimulated with phytohaemagglutinin, Sertaconazole significantly reduced the release of several proinflammatory cytokines compared with a range of other antifungal agents tested [17]. In the present study, the patients with grade 0 and 1 erythema in Clotrimazole group were 30% and 63.3% and in Sertaconazole group, the patients with grade 0 and 1 erythema were 96.7% and 0% after the treatment period [Table/Fig-1]. This shows that a significantly better reduction in erythema by Sertaconazole (p<0.02, [Table/Fig-1]). This can again be attributed to anti-inflammatory property and better clinical efficacy with Sertaconazole. Similarly in the sertaconazole group, post treatment period the results for erythema [Table/Fig-2], scaling [Table/Fig-3] and itching [Table/Fig-4] showed better results. After the treatment period, in Clotrimazole group the patients with grade 0 and 1 size were 43.3% and 26.7% and in Sertaconazole group were 56.7% and 43.3 % (table 5). Though the p value was not significant (>0.11, [Table/Fig-5]), there was better result with Sertaconazole. The results of KOH test in both the groups were negative in post treatment period [Table/Fig-6]. The pre-treatment values of both the groups in terms of erythema, scaling, itching, margins and size of the lesion and KOH mount were not significantly different [Table/Fig-7]. In order to compare the grading, the median grading in each of the parameters in each group was taken and after applying Mann Whitney U test, the p value was calculated which was insignificant [Table/Fig-7]. This shows that both the Clotrimazole and Sertaconazole groups were comparable in all parameters before treatment. This study also reveals that there was highly significant improvement in the patients receiving sertaconazole in terms of reduction of margins and itching [Table/Fig-8]. The mean difference and the standard deviation of total scores for Clotrimazole are 7.20 and 1.69 and for Sertaconazole group are 8.80 and 1.52 respectively [Table/Fig-9]. The p value is highly significant (p<0.001).

The above results signify that Sertaconazole 2% cream is better than Clotrimazole 2% cream in treating Tinea corporis. Most azole drugs are fungistatic, which, although limits fungal cell growth, does not prevent the shedding of viable mycelial cells from the skin surface. Sertaconazole however, has an additional fungicidal activity. In general, fungicidal drugs are preferred over fungistatic drugs for superficial dermatophyte infections because higher cure rates are achieved in shorter treatment times, thus increasing the likelihood of patient adherence and decreasing the incidence of recurrence [17]. One of the drawbacks of Sertaconazole may be the cost factor which may come down after some time.

The limitations of this study are the small sample size and the efficacy of creams was not evaluated in other forms of dermatophytosis like Tinea cruris, Tinea capitis, and Tinea unguinum. Further studies are needed to evaluate the efficacy of Sertaconazole in these other forms of Tinea infections and in larger sample size.

CONCLUSION

In the present study efficacy of 2% Sertaconazole cream was compared with 2% Clotrimazole cream applied topically for three weeks on the lesions of T Corporis. At the end of three weeks Sertaconazole showed a significant reduction in erythema, scaling and other parameters compared to Clotrimazole cream. Hence, Sertaconazole has a better antifungal efficacy.

REFERENCES

[1] World Health Organization.Laboratory manual for diagnosis of fungal opportunistic infections in HIV/AIDS patients. Geneva: World Health Organization:2009. p. 4-10.

[2] Jain A, Jain S, Rawat S. Emerging fungal infections among children: A review on its clinical manifestations, diagnosis, and prevention. *J Pharm Bioallied Sci.* 2010;2:314–20.

[3] Hay RJ, Ashbee HR. Mycology. In: Rook's textbook of dermatology. BurnsT, Breathnach S, Cox N, Griffiths Ceditors. 8th ed. Edinburgh: Wiley Blackwell. 2010;2:36.1-36.93.

[4] Wolff K, Goldsmith LA, Katz SI, Gilchrist BA, Pallar AS, Leffell DJ. Fitzpatricks dermatology in general medicine. 7th ed. *New York: McGraw Hill*; 2008. p. 1845-46.

[5] Tripathi KD. Essentials of Medical pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical publishers (p) Ltd; 2008. p.757-65.

[6] Wolverton SE. Comprehensive dermatologic drug therapy. Philedelphia: WB Saunders company. 2001; 24: p. 501-03.

[7] Borelli C, Klovekor G, Ernst TM, Bodeker RH, Korting HC, et al. Comparative study of 2% sertaconazolesolution and cream formulations in patients with Tinea corporis, Tinea pedis interdigitalis, or a corresponding candidiasis. *Am J Clin Dermatol.* 2007;8(6):371-78.

[8] Croxtall DJ, Plosker LG. Sertaconazole- A review of its use in the management of superficial mycoses in dermatology and gynaecology. *Drugs*. 2009;69(3):339-59.

[9] Milne LJR. Fungi. In: Collee JG, Marmion BP, Fraser AG, Simmons A editors. Practical Medical Microbiology.14th ed.*ChurchillLivingstone*;1996. 695-720.

[10] Palacin C, Sacristan A, Ortiz JA. Invitro activity of Sertaconazole. *Arzneimittelforschung.* 1992;42(5A):699-705.

[11] Drouhet E, Dupont B. In vitro antifungal activity of Sertaconazole. *Arzneimittelforschung.* 1992; 42(5A): 705-10.

[12] Carrillo-Munoz AJ, Quindos G, Del Valle O. In-vitro antifungal activity of Sertaconazole nitrate against recent isolates of Onychomycosis causative agents. *J Chemother*. 2008; 20(4):521-23.

[13] Carrillo-Munoz AJ, Guglietta A, Palacin C. In-vitro antifungal activity of Sertaconazole compared with nine other drugs against 250 clinical isolates of Dermatophytes and Scopulariopsis brevicaulis. *Chemotherapy.* 2004;50(6): 308-13.

[14] Martin-Mazuelos E, Aller AI, Morilla D. Antifungal activity ofSertaconazole in-vitro against clinical isolates of Candida spp. *Chemotherapy.* 1996;42(2):112-17.
[15] Alomar C, Bassas S, Casas M. Multi-centre double-blind trial on the efficacy and safety of Sertaconazole 2% cream incomparison with Miconazole 2% cream on patients suffering from cutaneous mycoses. *Arzneimittelforschung.* 1992;42(5A):767-73.
[16] Liebel F, Lyte P, Garay M. Anti-inflammatory and anti-itch activity ofSertaconazole nitrate. *Arch Dermatol Res.* 2006 ;298(4):191-99.
[17] Kyle AA, Dahl MV. Topical therapy for fungal infections. *Am J Clin Dermatol.* 2004;5(6):443-51.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, SS institute of Medical Sciences, Davangere, Karnataka, India.
2. Professor, Department of Pharmacology, J.J.M. Medical College, Davangere, Karnataka, India.
3. Professor, Department of Skin, J.J.M. Medical College, Davangere, Karnataka, India.
4. Assistant Professor, Karpagam Medical Sciences And Research Centre, Coimbatore, India.
5. Post Graduate, Department of Pharmacology, SS Institute of Medical Sciences & Research Centre, Davangere, Karnataka, India.
6. Professor and Head, Department of Pharmacology, SS institute of Medical Sciences, Davangere, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Raghu Prasada Malladar Shivamurthy,
#2846, 3rd E Main Road, SS Layout B Block, Davangere, Karnataka, India.
Phone : 09481672484, E-mail : raghuprasada@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 09, 2014**
Date of Peer Review: **Jul 21, 2014**
Date of Acceptance: **Aug 13, 2014**
Date of Publishing: **Sep 20, 2014**