DOI: 10.7860/NJLM/2016/23556:2167

Original Article

Pharmacology Section

Sertaconazole Nitrate 2% Cream for the Treatment of Tinea pedis

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ABSTRACT

Introduction: Tinea pedis is a superficial fungal infection of the skin of feet caused by dermatophytes and characterised by erythema, desquamation, itching, vesicles and pustules in the interdigital or subdigital area, over soles and sides of feet. It is usually treated with a topical antifungal agent. Sertaconazole is a new, wide-spectrum, third-generation imidazole topical antifungal agent, available in cream, solution, powder and microsponge formulations.

Aim: To study the effectiveness of 2% sertaconazole nitrate cream in patients of tinea pedis.

Materials and Methods: Clinically diagnosed and culture confirmed one hundred sixty seven patients of tinea pedis were included in the study group. They were prescribed 2% sertaconazole cream for the treatment phase of four weeks. After this, there was a follow-up phase of two weeks. Results were analysed at the end of follow-up phase.

Results: Clinical success was achieved in one hundred thirty four (134) patients and mycological cure in one hundred fifty seven (157), out of total one hundred sixty seven (167) patients included in the study group. Thus, 80.2% patients had no symptoms and signs and 94.0% patients had negative culture at the end of follow-up phase.

Conclusion: Sertaconazole nitrate 2% cream is effective and safe in the treatment of tinea pedis. Its anti-inflammatory and anti-pruritic activities enhance the efficacy of drug beyond dermatophyte eradication. Thus, it also improves quality of life of patients.

Keywords: Antifungal agent, Dermatophytes, Superficial mycotic infection

INTRODUCTION

Superficial mycoses are prevalent in the world. Its prevalence rate is 20-25 % in general population. Dermatophytes are the most common causative organisms of superficial mycoses [1-3].

Dermatophytosis is fungal infection of the skin. It is caused by dermatophytes of several different species which thrive on warm and moist skin. Dermatophytes of genera Trichophyton and Microsporum are the most common causative organisms. These fungi affect different parts of body and leads to Tinea pedis (fungal infection of feet), Tinea corporis (infection of arms, legs and trunk), Tinea cruris (groin area infection), Tinea manuum (hands and palm infection), Tinea capitis (infection of scalp), Tinea barbae (facial hair infection) and Tinea faciei (infection of face). T. corporis, T. cruris and T. pedis are the most common dermatophytoses [4].

Antifungal topical agents include miconazole, terbinafine, butenafine, clotrimazole, ketoconazole and tolnaftate. They have been recommended for the treatment of limited dermatophytosis. In more extensive cases oral therapy may be prescribed. Sertaconazole and luliconazole are new antifungal topical agents. Sertaconazole is benzothiopene imidazole derivative. It inhibits the synthesis of ergosterol in the fungal cell walls, which leads to disruption of mycelial growth and replication. At higher concentration, it binds directly to the non-sterol lipids of fungal cell walls, resulting in increased permeability and subsequent lysis of the mycelium. Thus, sertaconazole eradicates dermatophytes from the site of lesion [5].

Sertaconazole nitrate activates mitogen activated protein kinase – cyclooxygenase -2 – prostaglandin E-2 pathway with subsequent release of prostaglandin E-2. Thus, sertaconazole mediates its anti-inflammatory effect. The anti-pruritic acitivity of sertaconazole is mediated by inhibition of contact hypersensitivity and scratch responses. These additional properties of sertaconazole provide clinical benefit to the patients [6,7].

Adverse effects include burning, swelling, irritation, tenderness, discolouration and dry skin. Serious adverse effects blistering, open sores have been reported. A very serious allergic reaction is rare. The Minimum Inhibitory Concentration (MIC) of sertaconazole ranges from 0.06 to 1 µg/ml against a variety of dermatophytes [8].

The aim of the present study was to assess effectiveness of new antifungal topical agent sertaconazole (2%) cream in the treatment of tinea pedis.

MATERIALS AND METHODS

The present prospective study was conducted in the Out Patient Department of Skin and VD, Darbhanga Medical College and Hospital, Darbhanga on adult patients with tinea pedis during period of December 2015 to March 2016. The patients were explained in detail, about the nature of the study. Informed consent was obtained from each patient. The study was approved by institutional ethics committee.

Adult men and women, aged >18 years with fungal infection of feet, KOH mount positive for fungal elements in skin specimen by direct microscopic examination, and culture positive for dermatophytes in skin specimen were included in the study group. Patients were excluded if they had fungal infections of body other than feet, pregnancy, severe psychiatric illness, history of antifungal drugs/ immunosuppressive agents within four weeks, allergy to an azole antifungal or were lactating.

A detailed clinical history, local and systemic examination was done in all cases. After clinical assessment one hundred ninety two (192) patients were enrolled for the study. Clinical assessment was determined by assessment of symptoms and signs of Tinea pedis e.g. erythema, itching, desquamation, vesicles and pustules, with their intensity. They were scored on a scale of 0 = absent, 1= mild, 2= moderate, 3= severe. Total Composite Score (TCS) of symptoms and signs was calculated by adding up the individual score of each symptom and sign. Patients were eligible for the study if they had a total composite score of more than 6.

Skin scraping was collected by using a blunt scalpel. The lesion was firmly scraped, particularly at advancing borders, after cleaning it with 70% alcohol. The specimen of was subjected to KOH (potassium hydroxide) wet preparation of varying concentrations (10 to 20%) for the presence of fungal elements. KOH positive specimen was then inoculated for culture into two media, (a) Sabouraud's Dextrose Chloramphenicol actidione Agar, and (b) Sabouraud's Dextrose Cyclohexene Agar. The agar plates were then aerobically inoculated at 28°C for four weeks. Media were observed daily for growth of dermatophytes. Different species were identified macroscopically (colony morphology, pigmentation and growth rate) and microscopically (specific structure of different species of dermatophytes) supplemented by other tests (urease test, hair perforation test and rice grain test).

Culture positive one hundred sixty seven (167) patients were included in the study group and culture negative twenty five (25) patients were excluded from the study. Patients were advised to apply locally over the skin lesions 2% sertaconazole cream twice daily for four weeks during 'Treatment Phase'. After end of treatment phase, there was a 'Follow-up Phase' for two weeks. At the ends of 'treatment' and 'follow-up' phases, clinical assessments and laboratory investigations (KOH mount & dermatophyte fungal culture) were done. Clinical success (symptomatic relief plus clinical cure) and mycological success (eradication of pathogen) were evaluated at the end of follow-up phase. Reduction of the total composite score was calculated by difference between baseline and end of follow-up phase scores.

Primary efficacy parameters were based on reduction in symptoms /signs, and eradication of dermatophytes, confirmed by negative culture results. Secondary efficacy parameters were reduction in total composite score of at least 2 points, and reporting of adverse events.

STATISTICAL ANALYSIS

Data management and analysis were done using SPPS 20. Mean, SD (standard deviation), percentage (%), SEM (standard error of mean), 95% CI, t, q and p-values were calculated.

RESULTS

Total 167 patients were included in the study group, out of which 105 (62.9%) were men and 62 (37.1%) were women of mean age 29.6 years [Table/Fig-1].

Parameters n(%)	Value
Gender	
• Males	105 (62.9)
• Females	62 (37.1)
Age (years)	
• Mean (SD)	29.67 (12.89)

[Table/Fig-1]: Baseline demographics of study group patients. n = total number of study group patients, %= percentage, SD = standard deviation.

Primary Efficacy Parameters

At baseline erythema, desquamation and itching were present in all patients, while vesicles were present in 63 (37.7%) and pustules in 41 (24.5%) cases. At the end of treatment phase, erythema, desquamation and itching were present in 19 (11.4%), 18 (10.8%) and 13 (7.8%) cases respectively. At the end of follow-up phase, 134 out of 167 (80.2%) had no symptoms and signs, while erythema persisted in 11 (6.6%), desquamation 10 (5.9%) and itching in 12 (7.2%) cases. At the end of follow-up phase, 157 out of 167 (94.0%) patients had negative culture reports, while 10 (5.9%) patients remained culture positive [Table/Fig-2,3].

Secondary Efficacy Parameters

The mean changes in erythema, desquamation, itching, vesicles and pustules from baseline to the end of follow-up phase were 2.30, 2.34, 2.31, 0.89 and 0.55 respectively. The mean percentage reduction in total composite score from baseline to the end of follow-up phase was 97.88% ($p<0.001$, significant). Adverse event (mild irritation) was observed in 5 (2.9%) cases during first week. None of the patients discontinued treatment as it resolved spontaneously [Table/Fig-4,5].

Parameters	At baseline No. (%)	At 4th Week No. (%)	At 6th Week No. (%)
Clinical assessment			
• Erythema	167 (100.0)	19 (11.4)	11 (6.6)
• Desquamation	167 (100.0)	18 (10.8)	10 (5.9)
• Itching	167 (100.0)	13 (7.8)	12 (7.2)
• Vesicles	63 (37.7)	02 (1.2)	0 (0.0)
• Pustules	41 (24.5)	01 (0.59)	0 (0.0)
Mycological assessment			
• Culture positive	167(100.0)	23 (13.8)	10 (5.9)

[Table/Fig-2]: Proportion of patients with clinical features and positive culture status at baseline and the end of 4th and 6th weeks. (n=167).
n = total number of study group patients, No.= number of patients in each parameter, %= percentage.

Result	Not achieved		Achieved		95% CI		Total	
	No.	(%)	No.	(%)	Lower	Upper	No.	(%)
Clinical success	33	(19.76)	134	(80.23)	0.73	0.85	167	(100.0)
Myco-logical success	10	(5.99)	157	(94.01)	0.89	0.96	167	(100.0)

[Table/Fig-3]: Frequency of success with corresponding 95% CI in patients with Tinea pedis treated with 2% sertaconazole cream.
No.= number of patients in each parameter, %= percentage,CI = Confidence interval.

Parameters	At baseline		At 4th Week		At 6th Week	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Erythema	2.36	(0.58)	0.11	(0.10)	0.06	(0.06)
Desquamation	2.39	(0.58)	0.10	(0.09)	0.05	(0.05)
Itching	2.38	(0.53)	0.07	(0.07)	0.07	(0.06)
Vesicles	0.89	(0.20)	0.01	(0.01)	0	(0.0)
Pustules	0.55	(0.31)	0.005	(0.005)	0	(0.0)
Total	8 .51	(2.20)	0.29	(0.27)	0.18	(0.11)

[Table/Fig-4]: TotalComposite Score (TCS) of signs and symptoms at baseline, at the end of 4th week and at 6th week. (n=167).
n = total number of study group patients, %= percentage, SD = standard deviation.

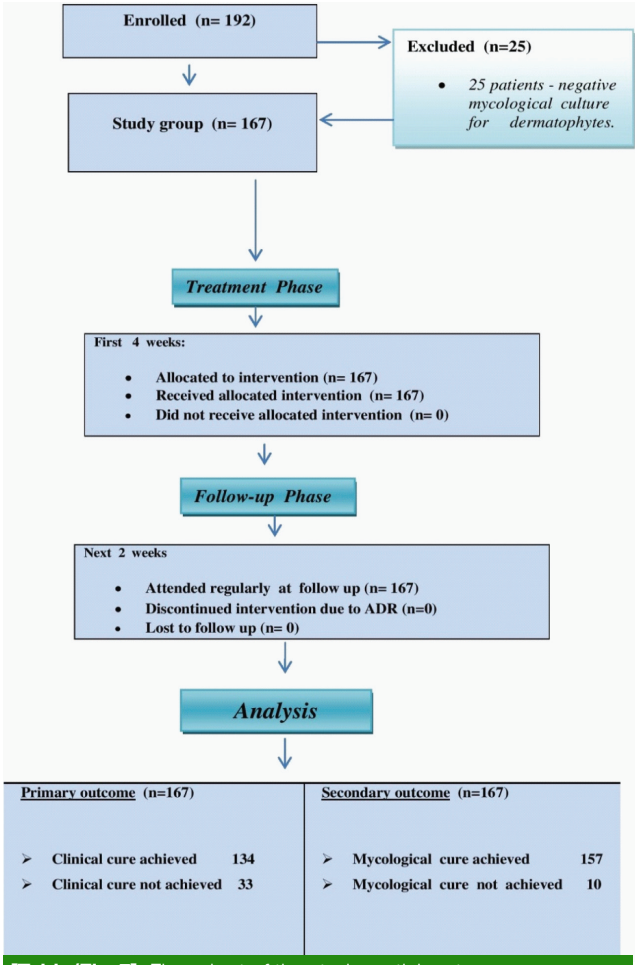
Pathogens

Trichophoton interdigitale was isolated in 101 (60.5%) cases and *Trichophoton rubrum* in 66 (39.5%) cases [Table/Fig-6].

The flow chart of the study participants has been presented in [Table/Fig-7].

Dermatophytes	No.	(%)
Trichophoton interdigitale	101	(60.5)
Trichophoton rubrum	66	(39.5)

[Table/Fig-6]: Dermatophytes isolated in Tinea pedis patients. (n=167)
n = total number of study group patients, No.= number of patients in which each dermatophyte species was isolated, %= percentage.



[Table/Fig-7]: Flow chart of the study participants.
n = number of patients, ADR = adverse drug reaction.

Comparison	Mean Difference	SEM	95 % CI		't'	'q'	p- value
			Lower	Upper			
At baseline vs At 4th week	8.22	0.17	7.89	8.54	58.62	82.90	*p <0.001
At baseline vs At 6th week	8.33	0.02	8.001	8.65	59.40	84.01	* p <0.001
At 4th week vs At 6th week	0.11	0.008	- 0.21	0.43	0.78	1.10	# p > 0.05

[Table/Fig-5]: Comparison of total clinical score at baseline vs 4th week, at baseline vs 6th week and at 4th week vs 6th week.
* = significant, # = not significant, SEM = Standard error of mean, CI = Confidence interval.

DISCUSSION

Present study was conducted on patients of Tinea pedis. Patients were treated with 2% sertaconazole topical cream applied twice daily for four weeks during treatment phase. Follow-up phase was for two weeks. Clinical success (symptomatic relief and clinical cure) was achieved in 80.2% cases. Negative culture test result (mycological success) was achieved in 94.0% cases. Relapse was not was observed in any case.

Borelli et al.,[9] reported 88.9% clinical success and 89.5% negative culture test in patients of Tinea pedis treated with 2% sertaconazole cream. Weinberg et al., [10] observed 100.0% freedom from erythema and 93.8% freedom from pruritus in patients with tineapedis treated with 2% sertaconazole cream. Shivamurthy et al., Jerajan et al., reported clinical success of 97.1% and negative culture report in 100.0% cases, while Bonifaz et al., observed 86.0% clinical and mycological cure in patients of Tinea pedis treated with sertaconazole cream 2% [11-13].

Present study observed mild irritation in 2.9% cases. Adverse event as mild contact dermatitis as been also been reported in 8.7% and 6.6% cases by Borelli et al., [4] and Chandana et al., [14] respectively with sertaconazole 2% cream. In both groups withdrawal of drug was not needed. No adverse event with 2% sertaconazole cream has been observed by Bonifaz et al., [13].

The present study observations also confirm that 2% sertaconazole cream is effective and safe in treatment of Tinea pedis. The clinical success and negative culture figures reported in present study are lower than previously reported.

LIMITATIONS

The limitations of the present study were strict inclusion/ exclusion criteria for selecting study group patients and relatively smaller sample size.

CONCLUSION

This study shows substantial benefit with sertaconazole nitrate 2% cream in the patients of tinea pedis. The outcomes are comparable with the previously published data. We believe that this is the first Indian study conducted in this humid and subtropical zone of East India. The results of present study indicate that sertaconazole eradicates dermatophytes from tinea pedis lesions in 94.0% cases and reduces total composite score by 97.88% at the end of follow-up phase. Quality of life is impaired in patients with tinea pedis because of pruritus and other symptoms and signs. It worsens with increasing severity of the tinea pedis. Sertaconazole has been observed in the present study to be effective in improving quality of life of patients by reducing symptoms and signs of tinea pedis. Adverse effect (mild irritation) was noted in 2.9% cases only. These observations are clinically significant. Thus, we conclude that sertaconazole cream 2% is effective as well as safe for the treatment of tinea pedis.

ACKNOWLEDGEMENT

We are grateful to all the participants who participated in the study.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Publishing: **Oct 01, 2016**