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Efficacy and tolerability of sertaconazole nitrate 2% cream vs. miconazole in patients with cutaneous dermatophytosis

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Summary

Sertaconazole is a new antifungal agent. To compare the efficacy and tolerability of sertaconazole and miconazole cream in cutaneous dermatophytosis, this prospective, randomized, multicentric comparative, phase 4 study was undertaken in 260 patients with cutaneous dermatophytosis after approvals from Institutional Ethics Committees. Patients were assigned to sertaconazole cream (2%) or miconazole cream (2%) topically twice daily for 2 weeks after obtaining informed consent. Efficacy variables included changes in mean scores of erythema, pruritus, desquamation, erythema/itching, burning/weeping, scaling/pustule and overall global assessment. Safety and tolerability were also assessed. A total of 122 patients in the sertaconazole group and 128 in the miconazole group completed the study with 10 drop-outs. There was a significant decrease ($P < 0.05$) in mean symptom scores and total scores from the first week onwards, sustained till 2 weeks and statistically significant ($P < 0.05$) in favour of sertaconazole. Moreover, 62.3% patients had complete clinical cure in the sertaconazole group ($P < 0.05$) compared with 44.6% in miconazole users. Both drugs were well tolerated and five patients in the sertaconazole group and nine in the miconazole group reported mild to moderate adverse events. Therapy with sertaconazole cream (2%) provided a better efficacy and tolerability compared with the miconazole cream (2%) and could thus be a therapeutic option in cutaneous dermatophytosis.

Key words: Sertaconazole, miconazole, cutaneous infections, dermatophytosis.

Introduction

Dermatophytoses, commonly known as ringworm or tinea, represent superficial fungal infections caused by dermatophytes, which are among the most common infections encountered in medicine. Dermatophytes are fungi that require keratin for growth. These fungi can cause superficial infections of the skin, hair and nails. Dermatophytes are spread by direct contact from other people, animals and soil as well as indirectly from fomites.[1] Drug classes available for treating tinea infections includes imidazoles, triazole, benzylamines, allylamines and hydroxypyridones. Topical antifungals clotrimazole, miconazole, terbinafine and tolfanate are safe and generally effective, but complete mycologic and clinical cures are difficult to achieve because relapses and chronic infections are common.[2]

The development of new antifungal agents has been marked by increasing pathogenicity of many fungal micro-organisms, the most important being emerging pathogens, the reduced sensitivity to traditional antifungal agents and seriousness of many mycoses.[7] Sertaconazole nitrate is a benzothiophene imidazole with a broad spectrum of action against yeast, dermatophytes, filamentous fungi and bacteria associated with cutaneous infections. The drug has both fungistatic and fungicidal activity. Its antibacterial activity extends to

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the types of Gram-positive bacteria that typically colonize these fungal infections of the skin and contribute to worsening of the regional inflammation, lesion appearance and clinical symptoms.[2]

This study was therefore undertaken to compare the efficacy, safety and tolerability of sertaconazole nitrate 2% cream and miconazole nitrate 2% cream in patients with cutaneous dermatophytosis.

Materials and methods

This clinical trial was conducted as a prospective multicentre (five centres) double- blind parallel- group randomized study in accordance with Declaration of Helsinki and its amendments, local laws and regulations. The study protocol, case-record form and the patient information sheet were approved by the respective Institutional Ethics Committees prior to any study procedure.

Male or female patients aged between 18–70 years with a clinical diagnosis of cutaneous dermatophytosis confirmed by microscopic examination [positive potassium hydroxide test (KOH)] were included in the study after obtaining their written informed consent. Female patients who were post-menopausal, surgically sterilized or having reliable method of birth control were included in the study. Patients willing to follow up during the study were also enrolled in the study.

Patients who were pregnant and lactating women, those who had received oral treatment with antimycotics during 4 weeks preceding the trial or topical treatment 1 week earlier, patients with chronic severe diseases, bacterial skin infection, therapy with topical antifungal agents within 14 days of study or oral antifungals within 3 months of study were excluded from the study. In addition, patients with a history of hypersensitivity to sertaconazole or those patients with any other condition which in the investigator's opinion did not justify his/her participation in the study were excluded.

Patients fulfilling the selection criteria were assigned randomly to two therapy groups in this study. One group received Sertaconazole nitrate 2% cream and the other received Miconazole 2% cream, both applied topically every 12 h.

The primary objective of the study was to assess the effectiveness and tolerability of sertaconazole nitrate (2%) cream and Miconazole nitrate (2%) cream in the treatment of cutaneous dermatophytosis. The primary end-point of the study was physician global assessment of clinical response regarding complete clinical cure at the end of 2 weeks. The secondary end-point was the clinical evaluation of the disease condition.

Overall Physician Global assessment of clinical response scale was determined at 2 weeks based on a successful treatment outcome determined by mycology negative and clinical cure.

Clinical evaluation of patient was performed at each visit for disease condition pruritis, erythema, desquamation, maceration according to clinical scale defined as 1 = much worse, 2 = worse, 3 = the same, 4 = better, 5 = much better, 6 = clinical cure.

Patients were examined at Baseline visit on day 0 and thereafter at weekly interval up to 2 weeks.

Patients were monitored for laboratory and clinical Adverse events (AEs) at each visit. All AEs or unexpected events were recorded in the case record forms. Patients were queried by the investigators for any AEs between study visits. The nature, date of onset, and duration of AEs were recorded. All investigator-reported clinical AEs were recorded at each study visit and evaluated by the investigator for intensity, seriousness and relationship to the study medication. Severity of an AE was graded by the investigator as follows: 1 = mild (awareness of sign or symptom but easily tolerated); 2 = moderate (discomfort enough to cause interference with usual activity); and 3 = severe (incapacitating, with inability to work or do usual activity). AEs that occurred within 7 days of the last study drug dose and serious AEs that occurred within 30 days of the last study drug dose were included in the safety analyses.

Routine investigations like haematology, biochemistry, ECG, X-ray chest and routine urine analysis were carried out at the beginning of study to rule out any serious medical illness.

Statistical analysis

The sample size calculation was based on complete cure rate at the end of 2 weeks assessed by physician with global clinical response scale. It was determined that at least 121 completed cases would be required in each arm to detect (with 80% power and a type 1 error at $\alpha = 0.05$ for two tailed) between-group difference of at least 20% in the percentage of patients with complete cure. More number of patients were enrolled (128 in sertaconazole group and 132 in the miconazole group) considering drop-out rate of 10% and to obtain that at least 121 patients would be available in each arm for the efficacy analysis. Between-group overall global assessments for clinical response and within- and between-group changes in pruritus, erythema and desquamation and adverse events were analysed by using Chi-square test while comparison of changes in mean scores of erythema/itching, burning/weeping

and scaling/pruritus and mean total scores between and within groups were compared using ANOVA Kruskall–Wallis test. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). All statistical tests for differences were two tailed with $\alpha = 0.05$. $P < 0.05$ was considered statistically significant. Data of mean scores were expressed as Mean (SD).

Results

A total of 260 patients with a clinical diagnosis of tinea corporis or tinea cruris were recruited and allocated to therapy with either sertaconazole nitrate 2% cream or miconazole nitrate 2% cream. Ten patients (six from sertaconazole group and four from miconazole group) were lost to follow-up and considered as drop-outs. A total of 250 (122 patients in sertaconazole group and 128 in the miconazole group) patients completed the study and were included in the efficacy analysis. The demographic data are depicted in Table 1.

Overall global assessment as per mycology assessment showed that of 122 receiving Sertaconazole, clinical cure was achieved in 76 (62.3%) patients and in only 57 (44.6%) patients receiving miconazole ($P < 0.05$) (Fig. 1).

At baseline the occurrence of pruritus, erythema and desquamation were similar in both the groups. However, by the end of the first week, 76.3% of the cases in the sertaconazole group reported improvement in their pruritus symptom to be better or much better when compared with only 49.2% in the miconazole group which was statistically significant ($P < 0.05$). By the end of 2 weeks therapy, clinical cure of pruritus was reported by 45.9% of the sertaconazole treated patients compared with 36.7% of the patients in the miconazole group (Table 2).

With regard to erythema, significantly ($P < 0.05$) greater number of patients (79.5%) in the sertaconazole group reported better to much better relief of erythema when compared with only 45.3% in the miconazole group by the end of the first week. Furthermore, the efficacy of sertaconazole was sustained even upto week 2 of therapy and significantly ($P < 0.05$) greater number of patients (51.6%) when compared with only 30.5% patients in the miconazole-treated group (Table 2).

Table 1 Demographic data of the patients.

Parameters	Sertaconazole nitrate	Miconazole
Patients	128	132
Age (mean)	37.40 (18–70 years)	36.56 (18–82 years)
Weight (mean)	61.45 (40–95 kg)	61.29 (40–89 kg)
Height (mean)	166.82 (150–184 cm)	167.94 (154–182 cm)
Sex (%)		
Male	107 (83.6)	110 (83.3)
Female	21 (16.4)	22 (16.7)

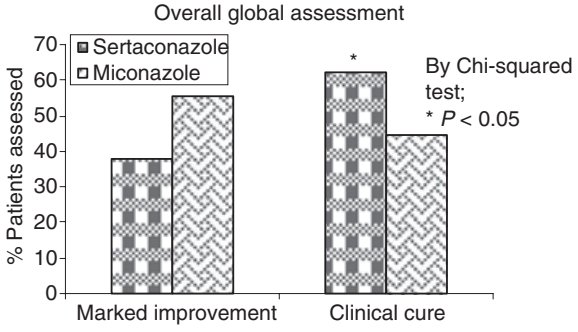

Figure 1 Overall global assessment of treatment with sertaconazole and miconazole.

A significantly greater ($P < 0.05$) number of patients (79.5%) reported improvement in desquamation and reported it to be better or much better following therapy with sertaconazole when compared with only 46.9% in the miconazole by the end of week 1. Moreover, the efficacy of sertaconazole was further sustained and by the end of the second week a significantly ($P < 0.05$) a greater number of patients (45.1%) in the sertaconazole group reported clinical cure when compared with only 22.7% patients in the miconazole group (Table 2).

Mean baseline scores of erythema/itching, burning/weeping and scaling/pustules were similar in the two groups prior to therapy. Following therapy, there was a statistically significant ($P < 0.05$) reduction of 36.3% in the sertaconazole group when compared with 22.3% in the miconazole group. The improvement was sustained till the end of the therapy and by week 2 the mean scores significantly ($P < 0.05$) improved by 73.3% in the sertaconazole group when compared with 69.6% in the miconazole group (Table 3).

Following therapy there was a significant ($P < 0.05$) reduction in burning/weeping scores by 44.3% when compared with 31.4% in the miconazole group. The improvement was sustained with the result that by the end of the second week the mean scores were improved by 77.3% in the sertaconazole group when compared with 64.4% in the miconazole group (Table 3).

There was a significant improvement in the scaling/pustules in 32.3% of the sertaconazole treated group when compared with only 26.7% in the miconazole group. Further improvements were observed at the end of the second week's therapy in the mean scores of scaling/pustules and the improve-

Table 2 Comparison of changes in pruritus, erythema and desquamation within and between the two groups.

	Sertaconazole nitrate			Miconazole		
Clinical scale	Basal (*N* = 122)	Week 1 (*N* = 122)	Week 2 (*N* = 122)	Basal (*N* = 128)	Week 1 (*N* = 128)	Week 2 (*N* = 128)
Pruritus						
Much worse	114 (93.4)	05 (04.1)	– (–)	120 (93.8)	07 (05.5)	– (–)
Worse	08 (06.6)	05 (04.1)	– (–)	08 (06.2)	04 (03.1)	– (–)
Same	– (–)	19 (15.6)	– (–)	– (–)	54 (42.2)	– (–)
Better	– (–)	44 (36.1)[1]	14 (11.5)	– (–)	63 (49.2)[1]	47 (36.7)
Much better	– (–)	49 (40.2)[1,2]	52 (42.6)	– (–)	– (–)	34 (26.6)
Clinical cure	– (–)	– (–)	56 (45.9)	– (–)	– (–)	47 (36.7)
Erythema						
Much worse	104 (85.2)	05 (04.1)	– (–)	121 (94.5)	07 (05.5)	– (–)
Worse	18 (14.8)	– (–)	– (–)	07 (05.5)	06 (04.7)	– (–)
Same	– (–)	16 (13.1)	– (–)	– (–)	57 (44.5)	06 (04.7)
Better	– (–)	38 (31.1)[1]	18 (14.8)	– (–)	54 (42.2)[1]	52 (40.6)
Much better	– (–)	59 (48.4)[1]	41 (33.6)	– (–)	04 (03.1)[1]	31 (24.2)
Clinical cure	– (–)	04 (03.3)	63 (51.6)[2]	– (–)	– (–)	39 (30.5)
Desquamation						
Much worse	118 (96.7)	09 (07.4)	– (–)	113 (88.3)	07 (05.5)	– (–)
Worse	04 (03.3)	– (–)	– (–)	15 (11.7)	10 (07.8)	– (–)
Same	– (–)	16 (13.1)	– (–)	– (–)	51 (39.8)	– (–)
Better	– (–)	41 (33.6)[1]	– (–)	– (–)	56 (43.8)[1]	63 (49.2)
Much better	– (–)	56 (45.9)[1,2]	67 (54.9)	– (–)	04 (03.1)[1]	36 (28.1)
Clinical cure	– (–)	– (–)	55 (45.1)	– (–)	– (–)	29 (22.7)

By Chi-square test: [1]within Group $P < 0.05$ significant, [2]between Group $P < 0.05$ significant.

ment was greater (78.3%) in the sertaconazole group when compared with 73.6%, although the difference between the two groups did not attain statistical significance (Table 3).

As a consequence of the improvement in mean scores of erythema/itching, burning/weeping, scaling/pustules, there was a significant improvement in the mean total scored at the end of week 1 by 37.3% in the sertaconazole group when compared with 27.2% in the miconazole group. By the end of the second week's therapy, the improvement continued and it was observed that there was a 74.1%improvement in the sertaconazole group when compared with 69.3% in the miconazole group (Table 4).

Both the drugs were well tolerated and only five patients (4.5%) in the sertaconazole group reported nine (8.2%) adverse events and nine (8.2%) patients in the miconazole group reported 12 (10.9%) adverse events. The most common adverse events were dry skin (two vs. four), erythema (one each), burning (three vs. two), itching (two vs. three), irritation (one each) and hyperpigmentation (zero vs. one) in the sertaconazole and miconazole group respectively. The causality of all

Table 3 Comparison of changes in mean scores of erythema/itching, burning/weeping and scaling/pustules after treatment within and between two groups.

	Mean score ($\bar{X}$ ± SD)	
Duration in weeks	Sertaconazole nitrate	Miconazole
Erythema/itching		
Baseline	2.51 ± 0.61	2.47 ± 0.66
1	1.60 ± 0.62[1]	1.92 ± 0.63[1,2]
2	0.67 ± 0.78[1]	0.75 ± 0.51[1,2]
Burning/weeping		
Baseline	1.85 ± 0.77	1.91 ± 0.78
1	1.03 ± 0.61[1]	1.31 ± 0.67[1,2]
2	0.42 ± 0.63[1]	0.68 ± 0.46[1,2]
Scaling/pustules		
Baseline	2.54 ± 0.71	2.58 ± 0.79
1	1.72 ± 0.62[1]	1.89 ± 0.66[1,2]
2	0.55 ± 0.75[1]	0.68 ± 0.48[1,2]

By ANOVA Kruskal--Wallis Test: [1]within Groups $P < 0.05$ significant, [2]between Groups $P < 0.05$ significant.

Table 4 Comparison of changes in mean total score after treatment between two groups.

	Mean total score ($\bar{X}$ ± SD)	
Duration in weeks	Sertaconazole nitrate	Miconazole
Baseline	7.64 ± 3.46	7.62 ± 4.01
1	4.79 ± 2.53[1]	5.55 ± 2.80[1,2]
2	1.98 ± 2.83[1]	2.34 ± 1.54[1,2]

By ANOVA Kruskal--Wallis Test: [1]within Groups $P < 0.05$ significant, [2]between Groups $P < 0.05$ significant.

Table 5 Profile of adverse events.

	Sertaconazole nitrate	Miconazole
Adverse events	*N* (%)	*N* (%)
Dry skin	02 (01.8)	04 (03.6)
Erythema	01 (00.9)	01 (00.9)
Burning	03 (02.7)	02 (01.8)
Itching	02 (01.8)	03 (02.7)
Irritation	01 (00.9)	01 (00.9)
Hyperpigmentation	–	01 (00.9)
No of pts	05 (04.5)	09 (08.2)
No of events	09 (08.1)	12 (10.9)

By Chi-square test $P > 0.05$ not significant.

the adverse events were possibly related to the study drugs. However, the adverse events were mild to moderate in severity and disappeared with continued therapy. None of the patients reported any serious adverse events or discontinued therapy as a result of the adverse events (Table 5).

At the end of the study, laboratory investigations like haemoglobin, total WBC count, platelet count, liver function tests like ALT and AST and Bilirubin and electrolytes like sodium and potassium were within normal limits and were not significantly different from the baseline levels.

Discussion

Effective topical therapy of superficial fungal infections is an important challenge in dermatological practice.[3,4] Topical antifungal agents often have a broad spectrum of action on dermatophytes and yeast, but the high relapse rates and recurrences of symptoms after stopping therapy are common clinical concerns.[5] Untreated or improperly treated superficial cutaneous fungal infections may become chronic and cause significant disability and morbidity.[5]

Sertaconazole nitrate is a topical broad spectrum antifungal that has been developed for the treatment of superficial cutaneous and mucosal infections. It has a dual mechanism of action. Firstly by inhibiting ergosterol synthesis through blockade of the P450-dependant enzyme pathway, it interferes with fungal cell growth. Secondly, it binds directly to the non-sterol lipids in the fungal cell membrane and thereby brings about leakage of the intracellular contents of the fungal cell and consequent death of the cell. Thus, sertaconazole is an effective fungicidal and fungistatic agent.[5]

The results of this study indicated that there was a significant decrease ($P < 0.05$) in the mean symptom scores as well as the total scores from the 1st week onwards and was sustained till 2 weeks in both the groups. The between group analysis was statistically significant in favour of sertaconazole at both time points. Moreover, 62.3% of the total cases had a marked to complete clinical cure in the Sertaconazole group which was significantly ($P < 0.05$) greater when compared with only 44.6% in the Miconazole users. These results are in agreement with those observed by other investigators.[5,6] It has been reported that in comparative studies, sertaconazole inhibited dermatophyte growth as well as or better than the other azoles.[7–10] The better efficacy of sertaconazole compared with miconazole could be because of the fact that the rank order of fungicidal effect in initial studies designed to compare the *in vitro* activity of several imidazoles was sertaconazole > miconazole > clotrimazole > ketoconazole.[5]

There was a significant improvement in the mean total scores of erythema/itching, burning/weeping, scaling/pustules by week 1 in the sertaconazole group compared with the miconazole group. This could be attributed to the anti-inflammatory properties of sertaconazole. Of the anti-fungal agents examined (butoconazole, ciclopirox olamine, fluconazole, miconazole nitrate, sertaconazole nitrate, terconazole, tioconazole and ketoconazole) only sertaconazole nitrate was found to significantly reduce the release of cytokines from activated lymphocytes and mitigate inflammation in animal models of irritant contact dermatitis and neurogenic inflammation.[11] In addition, sertaconazole nitrate inhibited contact hypersensitivity and scratching responses in a murine model of pruritus. Thus, topical administration of clinically relevant concentrations of sertaconazole nitrate resulted in an efficacious anti-inflammatory activity against a broad spectrum of dermal inflammation models and against itch.[11] The anti-inflammatory activity of sertaconazole may contribute to the efficacy of the drug in the treatment of cutaneous fungal conditions, particularly those cases associated with pronounced inflammation, as evidenced by the presence of erythema pruritus, and scaling. As result of such symptoms, topical corticosteroids are often added to anti-fungal therapy to provide rapid symptomatic relief. However, the potential for steroid-induced skin atrophy can limit the therapeutic use of an anti-fungal/steroid combination therapy. Thus, the presence of an anti-inflammatory and anti-itch action by sertaconazole nitrate may contribute to symptom relief and may obviate the need to add a topical corticosteroid in some patients.

Clinical safety and efficacy of sertaconazole nitrate on seborrheic dermatitis, versicolor, cutaneous candidiasis or dermatophytosis have also demonstrated that serta-

conazole has comparable or superior efficacy to other imidazole anti-fungal agents such as miconazole, clotrimazole and ketoconazole, with a better clinical safety profile.[12] In this study, most of the adverse events were mild to moderate in intensity and included localized adverse events such as burning, itching and irritation. None of the patients reported any serious adverse events or discontinued therapy because of the adverse events. No significant changes were observed in any of the laboratory parameters at the end of the study. The results of this study suggested the good safety and tolerability profile of sertaconazole nitrate 2% cream. Sertaconazole is reported to be well suited for topical administration as evidenced by its good safety profile, low systemic absorption and long-lasting cutaneous retention.[11]

Thus in conclusion, the results suggested of this study indicated that therapy with the sertaconazole cream (2%) provided a better efficacy and tolerability compared with miconazole cream (2%) and could thus serve as a better therapeutic option in cutaneous dermatophytoses.

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