



## COMPARATIVE EVALUATION OF NEWER TOPICAL ANTIFUNGAL AGENTS IN THE TREATMENT OF SUPERFICIAL FUNGAL INFECTIONS (TINEA OR DERMATOPHYTIC)

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### ABSTRACT

Within the past few years, new extended-spectrum triazoles and allylamines have been introduced into market. Few of them include Luliconazole, Sertaconazole and Amorolfine. It is a multicentric, randomized, open-label, comparative study to evaluate the efficacy of newer antifungal drugs. A total 150 patients needed to be enrolled in the study based on the inclusion and exclusion criteria. All the patients are aged between 18 to 80 years. Patients above the age of 18 with clinical evidence of cutaneous mycoses (commonest presentation- tinea corporis) were treated with newer antifungals like Luliconazole, Sertaconazole, Amorolfine and eberconazole and Terbinafine and a potassium hydroxide (KOH) preparation of scrapings from a selected lesion was examined microscopically and clinically evaluated. The symptoms and signs of erythema, scaling and pruritus were scored on a scale of 1 (nil) to 3 (severe). Patients were eligible for the study if they had a combined score of at least 5. Sertaconazole showed higher efficacy with 93.3% ( $p < 0.05$ ) and also found to produce least percentage of adverse events with 6.6% compared to other antifungals. Sertaconazole proved to be highly efficient compared to other newer antifungals in terms of efficacy and safety.

**KEYWORDS:** Sertaconazole, Luliconazole, Amorolfine, ketoconazole, Efficacy and Safety

### INTRODUCTION

Dermatophyte infections are one of the earliest known fungal infections of mankind and are very common throughout the world<sup>1</sup> (Venkatesan *et al*, 2007). Although dermatophytoses does not cause mortality, it does cause morbidity and poses a major health problem (Emmons *et al*, 1974) especially in tropical countries like India due to the hot and humid climate<sup>2</sup>. No race in any geographical location is totally free from dermatophytoses (Rippon *et al*, 1985)<sup>3</sup>. Given that, the degree of immunosuppression and the number of immunosuppressed patients are increasing at an unprecedented pace, the management of dermatophytoses would be a definite challenge to mankind in the years to come.

So many topical antifungal agents have been introduced that it has become very difficult to select the proper agent for a given infection. Topical treatment of fungal infections took a step forward in the 1960s with the introduction of biologically active agents with specific antifungal mechanisms of action. Nonspecific agents have been available for many years, and they are still effective in many situations. These agents include Whitfield's ointment, Castellani paint, gentian violet, potassium permanganate, undecylenic acid and selenium sulfide. Specific antifungal agents include, among others, the polyenes (nystatin, amphotericin B), the imidazoles (metronidazole, clotrimazole) and the allylamines (terbinafine, naftifine). Most modern broad-spectrum antifungal agents act by blocking specific steps in the synthesis of fungal cell membrane components. Although the choice of an antifungal agent should be based on an accurate diagnosis (Weitzman *et al*, 1995)<sup>4</sup>

Most Tinea corporis, Tinea cruris, and Tinea pedis infections can be treated with topical agents. Consideration should be given to systemic treatment when lesions covering a large body-surface area fail to clear with repeated treatment using different topical agents. In treating dermatophytosis, the physician must also address environmental factors that lead

to or exacerbate Tinea infection and select an appropriate topical therapy for the infection. The antifungal agents can be grouped by structure and mechanism of action. The two principal pharmacologic groups are the azoles and the allylamines. When treating a dermatophyte infection, it is unlikely that the physician will know the infecting species. In general, Tinea corporis and Tinea cruris require once- to twice-daily treatment for two weeks. Tinea pedis may require treatment for four weeks. Treatment should continue for at least one week after symptoms have resolved. Currently, topical azoles and allyl amines are used for the treatment of Cutaneous mycoses with disadvantages like long duration of therapy, which leads to poor compliance and a high relapse rate. Some of the newer agents require only once-daily application and shorter courses of treatment, and are associated with lower relapse rates (Baran *et al*, 2007)<sup>5</sup>. There are no studies comparing drugs on which to base a recommendation for drugs of choice. Studies are needed to evaluate the clinical efficacies and cost advantages of both newer and traditional agents.

Within the past few years, new extended-spectrum triazoles and allylamines have been introduced into market among such are Luliconazole, Sertaconazole, eberconazole which belong to triazoles and Amorolfine which belong to Allyamine group. This report will summarize the studies evaluating new antifungal agents that are approved by the US Food and Drug or that have completed phase 3 clinical trials Administration (Spanakis *et al*, 2006)<sup>6</sup>

The main aim of the study is to compare the efficacy of newer antifungals like Luliconazole, amorolfine, eberconazole, sertaconazole and terbinafine cutaneous mycoses (commonest presentation- *Tinea corporis*). The study also aims to evaluate the effectiveness and safety of these newer topical antifungals.

## PATIENTS AND METHODS

Patients were recruited from the skin OPD at the Omni Hospitals, Hyderabad between February and August 2011. The study was approved by the Institutional Human Ethics Committee. A written informed consent was obtained from the patients prior to study enrollment.

### Patient Selection

Patients above the age of 18 with clinical evidence of cutaneous mycoses (commonest presentation-Tinea corporis) were clinically evaluated and a potassium hydroxide (KOH) preparation of scrapings from a selected lesion was examined microscopically. The symptoms and signs of erythema, scaling and pruritus were scored on a scale of 1 (nil) to 3 (severe). Patients were eligible for the study if they had a combined score of at least 5. Women who were pregnant or lactating were excluded. Patients with a known history or clinical evidence of severe cardiac, pulmonary, gastrointestinal, renal, hepatic or neurological disease and uncontrolled diabetes mellitus were also excluded from the study. Other reasons for exclusion were a known hypersensitivity to allylamine/benzylamine agents, treatment with systemic antifungal agents in the previous one month, itraconazole in the previous 6 months, systemic antibiotics in the previous 2 weeks, corticosteroids or immunosuppressants in the past 6 weeks, or any investigational drug in the previous 3 months.

### Drug Administration

After recruitment, patients were randomly assigned to receive Luliconazole, Sertaconazole, Amorolfine, Eberconazole, Terbinafine cream in blocks of 30 patients. On the first presentation each patient's demographic data including age, sex, baseline clinical parameters such as erythema, desquamation, pruritis, vesicles, and encrustation needed to be noted. The individual scores were added and total score was reported. A KOH (10%) preparation of the scraping was examined to confirm the presence of hyphae.

### Treatment

Patients will receive the newer antifungals randomly and the test product needed be applied once daily for 1 week in patients with Tinea cruris/ Tinea corporis and for 2 weeks in patients with Tinea pedis.

### Follow Up

The first follow up will be at 1 week and all the patients will be evaluated for clinical parameters and global clinical response. The second follow up is at 4 weeks and all the patients are again needed to be assessed for the parameters. Adverse events were recorded at each visit.

### Efficacy Parameters

The efficacy is assessed based on the following parameters: 1) KOH test: A negative KOH preparation at the end of the study period was considered as mycological cure. 2) Change in the signs and symptoms score.

## Statistical Analysis

The last observation carried forward (LOCF) method was used to analyze the data. Patients who had completed at least 2 weeks of therapy were included in the analysis. The data obtained was represented as mean  $\pm$  SEM and percentages, as applicable. Drug data and patient characteristic data were computed using MS Excel version 2007 and Graph pad prism 5.04 and Graph pad Instant 3.10 statistical package. Appropriate statistical tests (One way Analysis of Variance, ANOVA) were used for determining association between variables. A difference was considered as significant if the P value was less than 0.05.

## RESULTS

In total 150 patients were included into the IIT population, divided into five groups of 30 patients and received Amorolfine (E), Sertaconazole (D), Luliconazole (C), eberconazole (B), Terbinafine (A). A study population included 93 (62.0%) male patients and 57 (38.0%) female patients, the youngest patient was 18 years and the oldest was 58 years. Baseline characteristics of the IIT population are summarized in Table - 1. Overall mean changes in signs and symptoms were described in Table - 2. Mean of Signs and symptoms at different durations compared to baseline are given Figure - 1. Mean of Signs and symptoms at different durations compared to baseline done by One way ANOVA followed by post hoc Bonferroni's multiple comparison test. Mean changes in signs and symptoms compared to Terbinafine was done by One Way ANOVA followed by post hoc Dunnett's Multiple comparison test and there was no significant changes observed compared to Terbinafine group were described in Figure - 2. The efficacy is assessed by the number of patients who has maximum improvement in signs and symptoms and those who has complete cure and the results were presented in Figure - 3. Sertaconazole is showing higher efficacy with 93.3% followed by Luliconazole, Amorolfine, Terbinafine and eberconazole with efficacy 86.6%, 83.3%, 80.0% and 73.3% respectively. Safety is assessed by the number of adverse events and the results were presented in Figure - 4. A total of 25 patients that is 16.6% of cases had adverse events after the treatment. Out of these maximum were Burning, Irritation, Peeling of skin, Itching and Hyperpigmentation. Not a single patient discontinued the treatment because of adverse events. The safety of different treatments is given in Table - 4. Eberconazole is having maximum adverse events with 26.6% followed by Luliconazole, Terbinafine, Amorolfine and Sertaconazole.

## DISCUSSION

All the drugs were well tolerated, but Sertaconazole proved to be significantly more effective in terms of clinical improvement and in the eradication of fungal pathogens. The present study results reveals that Sertaconazole is having higher clinical symptom cure with 93.3%, in supporting to a study of Sharma *et al.*, 2009 comparing sertaconazole with miconazole, Sertaconazole showed 62.3% of clinical cure ( $P < 0.05$ ) compared with 44.6% in miconazole users<sup>7</sup>.

Table - 1 Baseline demographics and disease characteristics (intent-to-treat population)

	A group	B group	C group	D group	E group	Total
Sex, n (%)						
Male	19 (62.0)	24 (80.0)	21 (70.0)	22 (73.3)	21 (70.0)	93 (62.0)
Female	11 (36.6)	6 (20.0)	9 (30.0)	8 (26.6)	9 (30.0)	57 (38.0)
Age ( years)						
mean ± SD	28.5 ± 8.64	28.6 ± 6.48	32.8 ± 10.7	30.9 ± 10.4	30.8 ± 7.79	30.4 ± 8.99
median	25.5	27.5	31.0	29.5	29.0	28.0
Type of Infection, n (%)						
T.corporis	19 (63.3)	17 (56.6)	15 (50.0)	17 (56.6)	18 (60.0)	86 (57.3)
T.cruris	11 (36.6)	13 (43.3)	15 (50.0)	13 (43.3)	11 (36.6)	63 (42.0)
T.pedis					1 (0.03)	1 (0.006)
Mycological examination positive <sup>a</sup> , n (%)	30 (100.0)	30 (100.0)	30 (100.0)	30 (100.0)	30 (100.0)	150 (100.0)
Total diseased surface (cms) <sup>b</sup>						
mean ± SD	24.0 ± 14.4	26.0 ± 14.9	28.7 ± 15.9	24.6 ± 5.4	26.2 ± 5.9	35.9 (15.2)

Table 2 Overall Mean changes in signs and symptoms

Signs and Symptoms	Terbinafine (mean±SD )	Eberconazole (mean±SD )	Luliconazole (mean±SD )	Serconazole (mean±SD )	Amorolfine (mean±SD )
Erythema	0.79±0.68	0.96±0.65	0.78±0.72	0.67±0.78	0.74±0.71
Desquamation	1.08±0.64	1.13±0.62	0.93±0.69	0.93±0.80	1.02±0.75
Pruritus	0.84±0.58	0.77±0.41	0.77±0.62	0.74±0.69	0.75±0.53
Vesicles	0.22±0.29	0.24±0.28	0.19±0.35	0.20±0.39	0.22±0.38
Encrustation	0.05±0.09	0.06±0.11	0.08±0.16	0.06±0.13	0.09±0.16

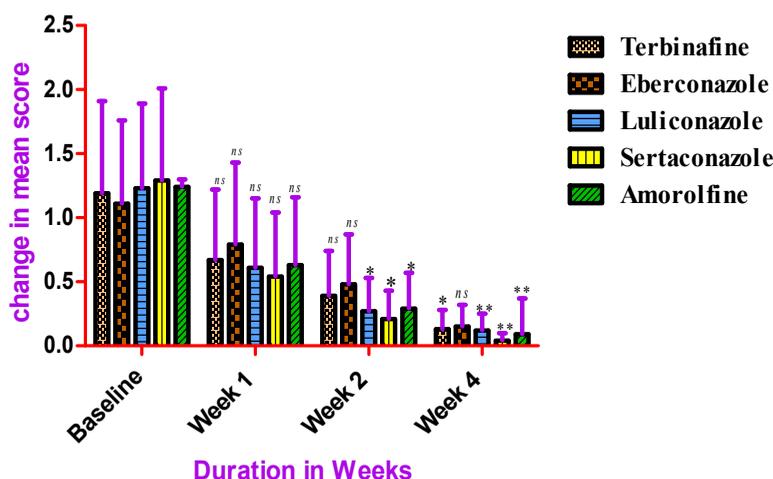


Figure - 1 Mean of Signs and Symptoms at different durations compared to baseline

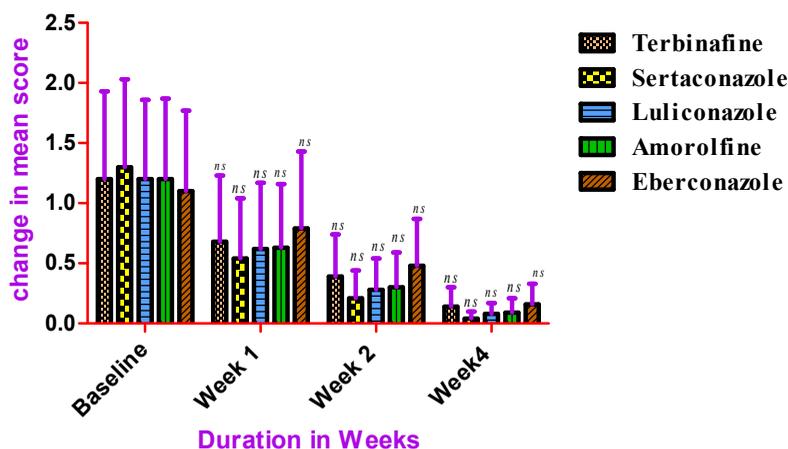


Figure - 2 Mean of Signs and Symptoms compared to Terbinafine

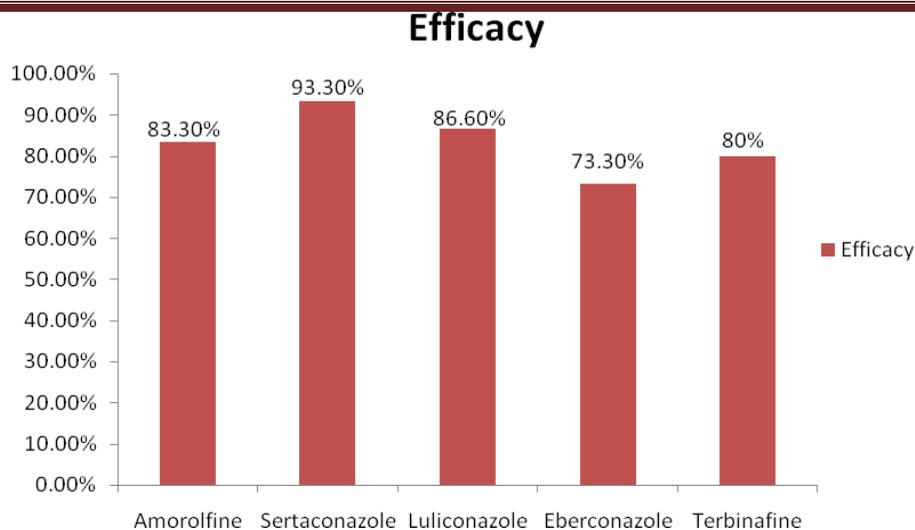


Figure - 3 Efficacy comparison between treatment groups

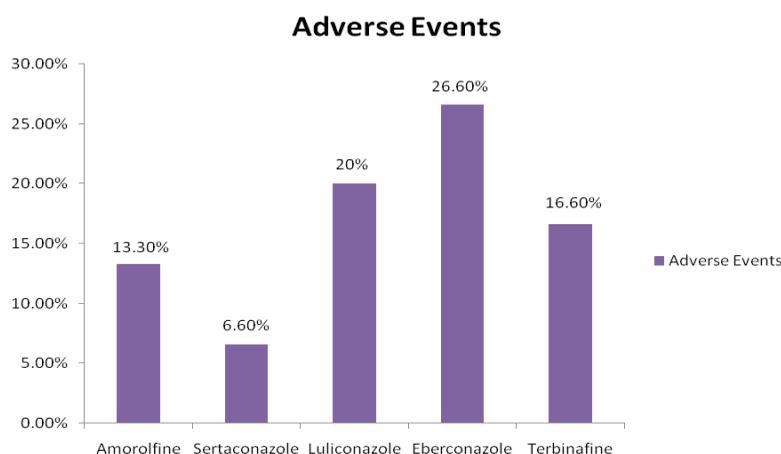


Figure - 4 Adverse events percentages in treatment groups

Luliconazole is having clinical symptom cure of 86.6% there is not much percentage difference compared to a previous study with different concentrations like 0.5%, 1% and 0.1% the rates of improvement in skin lesions were 90.5%, 91.0% and 95.8%, respectively showing greater efficacy rates (Watanabe *et al.*, 2007)<sup>8</sup>. In a study comparing Amorolfine and terbinafine, the Amorolfine-terbinafine combination showed higher response compared with the terbinafine group (66.7% vs. 53.5%, respectively;  $P < 0.04$ ). In the present study Amorolfine and Terbinafine is having clinical symptom cure percentage of 83.3% and 80%.

Adverse events reported were mild & did not report in the discontinuation of the drug. In a study of Bonifaz *et al.*, Sertaconazole reported AEs was low (8.7%) & none were considered serious (Bonifaz *et al.*, 2000)<sup>9</sup>. In the present study the adverse event reported with Sertaconazole was 6.6% which was very mild. In a study of Palacio *et al.*, with Amorolfine the AEs reporting was 13% which was comparable to that of present study which resulted in 13.3% (Palacio *et al.*, 2006)<sup>10</sup>. In another study of Palacio *et al.*, with Eberconazole resulted withdraw of two patients due to side effects, in the present study it accounted for 26.6% but didn't result in the withdrawal of patients (Palacio *et al.*, 1995)<sup>11</sup>.

In the present study the order of improvement in signs and symptoms in the Sertaconazole group was with pruritus followed by erythema and desquamation which is comparable to the study of Budimulja *et al.*, 2008 substantial improvement in signs and symptoms after 4 weeks of treatment 63.7% (58/91) were free of erythema, 33.0% (30/91) were free of desquamation, and 91.2% (83/91) were free of itch (Sudipdas *et al.*, 2010)<sup>12,13</sup>.

#### CONCLUSION

Sertaconazole proved to be highly efficient compared to other newer antifungals in case of efficacy and with lesser adverse events. It has also been shown that sertaconazole can kill *Trichomonas vaginalis* in vitro. The exact mechanism of action is as yet unknown. Sertaconazole also appears to inhibit the dimorphic transformation of *Candida albicans* into pathogenic fungi. Side effects were rarely reported with sertaconazole therapy, but may include contact dermatitis, burning on application site and skin dryness. Sertaconazole has also anti-inflammatory and antipruritic action. It inhibits the release of proinflammatory cytokines from activated immune cells. It has been shown that sertaconazole activates of the p38/COX2/PGE2 pathway. PGE2 can have a variety of important effects in the body including activation

of the body's fever response. Sertaconazole also has antibacterial action. It is hypothesized that the mechanism of action again involves sertaconazole's ability to form pores by mimicking tryptophan.

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