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Comparative Study of Luliconazole and Terbinafine Antifungal Drug

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ABSTRACT

Fungal infection of the skin is a significant public health problem. Tinea corporis & cruris of the skin respond well to topical antifungal therapy. Luliconazole is one of those drugs offering good efficacy & tolerability with a short duration of treatment. Terbinafine, an allylamine acts by selective inhibition of fungal squalene epoxidase. Luliconazole, an imidazole antifungal agent is considered to be more effective in inhibition of ergosterol biosynthesis, and its reservoir property in stratum corneum is greater than that of terbinafine. As there is a lack of studies between terbinafine & luliconazole, the present study was undertaken to compare the clinical efficacy in tinea corporis/tinea cruris patients.

INTRODUCTION

The fungal infection has become a major health predicament and can be categorized as superficial or invasive.[1] Superficial fungal infection is mainly due to dermatophytes, *Candida*, and *Malassezia* spp infection[2,3]. Dermatophytes can be called common for a group of three types of fungus that commonly causes skin infection/disease in human and animals. These mold genera are ***Microsporum***, ***Epidermophtyon,*** and ***Trichophyton***. There are approximately 40 different species of dermatophytes, in which the most common is the ***Trichophyton Ruburm***. Dermatophytes commonly cause infection of skin, hairs, and nails. The meaning of the word tinea is snake like appearance**.**

Type of infections

- Tinea pedis or athlete's foot
- Tinea cruris or jock itch
- Tinea corporis or ringworm of the body
- Tinea faciei of facial ringworm
- Tinea capitis or scalp ringworm
- Tinea manuum or ringworm of the hands
- Onychomycosis or ringworm of the nail
- Tinea incognito

Amongst all **tinea pedis, tinea cruris** and **tinea corpora** are the most common fungal infection that occurs in humans and animals.[4]

1) Tinea corporis

Tinea corporis is caused by common organisms including *Trichophyton mentagrophytes* and *Micosporum canis*. Tinea corporis is a dermatophyte infection of the skin excluding the hairs, nails, palms, soles, and groin. The characteristics of the typical lesion are an annular (circular lesion), well defined margins advancing centrifugally, presenting with scale, and often vesiculation. The center of the lesion is less scaly where organisms are cleared by the host immune response.[5]

2) Tinea cruris

Tinea cruris is similar to Candidal intertrigo, which is an infection of the skin by *Candida albicans*. Tinea cruris is a dermatophyte infection of the inguinal region, involving the inner aspect of the thigh and crural fold. It is commonly called as Jock itch. Sometimes it may extend onto the abdomen and buttocks. It occurs when ambient temperature and humidity are high.[6]

3) Tinea pedis

Tinea pedis is caused by fungi such as *Epidermophyton floccosum* or fungi of the genus *Trichophyton* including *T. rubrum* and *T. mentagrophytes*. Tinea pedis infection can be seen between the toes and may spread to the foot. In some cases, the infection may progress into a vesiculobullous pattern in which small, fluid filled blisters are formed. The lesion may be accompanied by peeling, maceration, and also by itching. [4]

The development of antifungal agent containing the imidazole group has led to significant improvement in the treatment of superficial and deep mycoses, as they possess higher efficacy and low toxicity.[2,3] Several topical imidazoles are currently available in the market that includes Clotrimazole, Bifonazole, Butoconazole, Econazole, Isoconazole, Ketoconazole, Miconazole, Sertaconazole, and Luliconazole.[3] Luliconazole (LLCZ) is relatively a new topical optically active, broad spectrum imidazole anti-fungal drug.[7] The main aim of the study is to compare the efficacy of newer antifungals like luliconazole, terbinafine, lanoconazole, sertaconazole, econazole.[8] Imidazole also alters the synthesis of triglycerides and phospholipid, which leads to an accumulation of toxic levels of hydrogen peroxide within fungal cells.[9] However, current imidazole antifungals have some limitations: conventional use has produced fungal resistance and many agents require treatment for several weeks, which could contribute to patient nonadherence, and ultimately disease recurrence.[10]

Classification of Antifungal drugs

Antifungal drugs are classified as:

1] Polyenes:-

Amphotericin B, Candicidin, Filipin, Hamycin, Nystatin, Natamycin, Rimocidin

2] Azole:-

- **Imidazoles-**

Luliconazole, Bifoconazole, Butoconazole, Clotrimazole, Econazole, Isoconazole, Fenticonazole, Ketoconazole, Miconazole, Omoconazole, Oxiconazole, Sertaconazole, Sulconazole, Tioconazole

- **Triazoles –**

Albaconazole, Epoxiconazole, Fluconazole, Isavuconazole, Itraconazole, Propiconazole, Ravuconazole, Terconazole, Voriconazole, Eficonazole

- **Thiazoles-**

Abafungin

3] Allylamines:-

Amorofin, Butenafine, Naftifine, Terbinafine

4] Echinocandins:-

Anidulafungin, Caspofungin, Micafungin

5] Others:-

Aurones, Benzoic acid, Ciclopirox, Flucytocine, Griseofulvin, Haloprogin, Tolnaftate, Undecylenic acid, Triacetin, Crystal violet, Orotomide, Miltefosine, Potassium iodide, Nikkomycin, Sulfur, Acrisorcin, Selenium disulfide, Sodium thiosulfate.[11]

AZOLE ANTIFUNGAL AGENTS

Azole antifungal agents is a group of medicine that contains an azole ring and inhibits the growth of a wide range of fungi. Azole antifungal agents could be used to treat the fungal infection of the body and skin, including athletes foot, onychomycosis, ringworm.[12]

Mechanism of action of azoles in the fungal cell wall [13]

The important biochemical difference between mammalian cells and the fungal cell wall is the presence of ergosterol in fungi whereas cholesterol is present in the mammalian cells. The fungal cell wall is made up of chitin which is composed of N-acetyl glucosamine and this

chitin confers rigidity to the cell wall whereas, most bacteria contain peptidoglycan in its cell wall.[14] [i]Understanding these biochemical differences in the cell structure helps in the development of antifungal drugs. In the fungal cell, acetyl CoA forms the building block for the synthesis of ergosterol. Acetyl CoA is converted into intermediates like HMG CoA, mevalonate, and squalene. Squalene is converted to lanosterol by the action of squalene epoxidase. This step is inhibited by allylamines and benzylamines. Lanosterol is converted by 14 *α – Lanosterol demethylase* to ergosterol, the important sterol of the fungal cell membrane. This step is inhibited by group imidazoles and triazoles drugs.[15]

Classification of azole antifungal

(1) Imidazoles

(2) Triazoles

Chemistry of Azole[16]

They are synthetically derived compounds and the azole nucleus is a five membered ring with nitrogen atoms. Depending upon the number of nitrogen atoms they are classified into two groups, Imidazoles, and triazoles.

- Imidazoles have 2 nitrogens in their azole nucleus.
- Triazoles have 3 nitrogen atoms.

IMIDAZOLES

Imidazoles are a broad group of antifungal medications. In this group, certain medications like clotrimazole have been around for decades, while others like sertaconazole, are recently available. The suitable topical agent is selected depending upon cost and availability.

Mechanism of action of imidazoles

Imidazoles inhibit lanosterol 14α-demethylase, a cytochrome P-450 dependent enzyme, which converts lanosterol to ergosterol. Depletion of ergosterol results in membrane instability and hyperpermeability thus, inhibition of growth and ultimately death.[17]

LULICONAZOLE (LLCZ)

Luliconazole is relatively a new topical optically active, broad spectrum imidazole antifungal drug.[7] Luliconazole {(-)-E-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazole-1-yl) acetonitrile} is a novel imidazole antifungal.[8] Luliconazole is uniquely characterized by its R-enantiomer side chain in addition to one chiral center.[18] Luliconazole has been shown to have antifungal activity against dermatophytes and candida *in vitro* and has been clinically assessed for the treatment of tinea pedis, cruris, and corporis.[9]

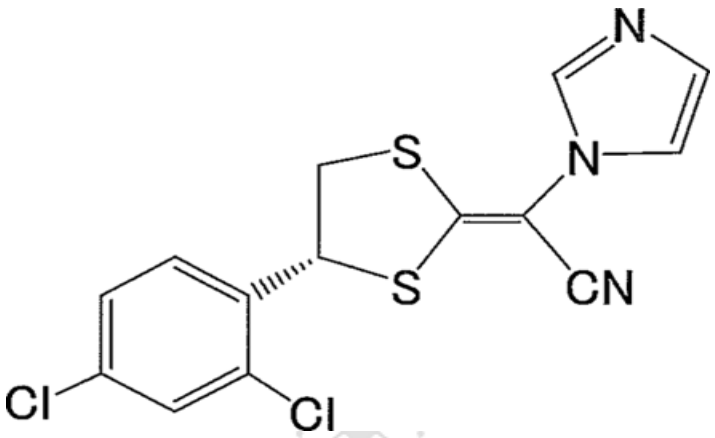

Figure No. 1: Structure of Luliconazole [19]

ALLYLAMINES

Naftifine was reported to be the first synthetic allylamine antifungal drug in 1985, it was the first commercially available allylamine in the market. It was synthesized from heterocyclic spiro-naphthalenones by acid hydrolysis. Then, terbinafine was developed by modification of naftifine and became the second allylamine with a significant antimycotic effect. [20]

Chemistry

These antifungals have a nitrogen atom having a neighboring double bond.

Mechanism of action

They reduce the synthesis of ergosterol by inhibition of *squalene epoxidase*. It is an enzyme that converts squalene to squalene epoxide. Reduced ergosterol results in membrane instability and hyperpermeability. They are fungicidal. Both are independent of the cytochrome P-450 enzyme system. They demonstrate the anti-inflammatory activity by inhibition of chemotaxis, and inhibition of *lipoxygenase*.[21]

TERBINAFINE

(E)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine;hydrochloride[22]

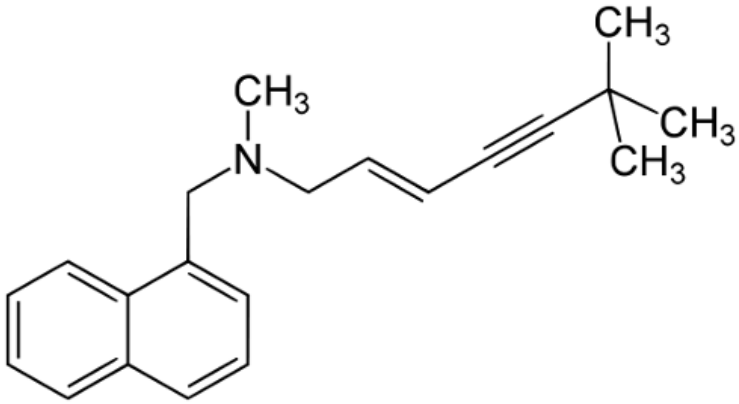

Figure No. 2: Structure of Terbinafine[23]

Terbinafine belongs to the allylamine class of antifungal agents. It is not part of the cytochrome P-450 superfamily. It is fungicidal to dermatophytes[24,25] Terbinafine exhibits fungicidal action against dermatophytes, *Aspergillus* species.[26]

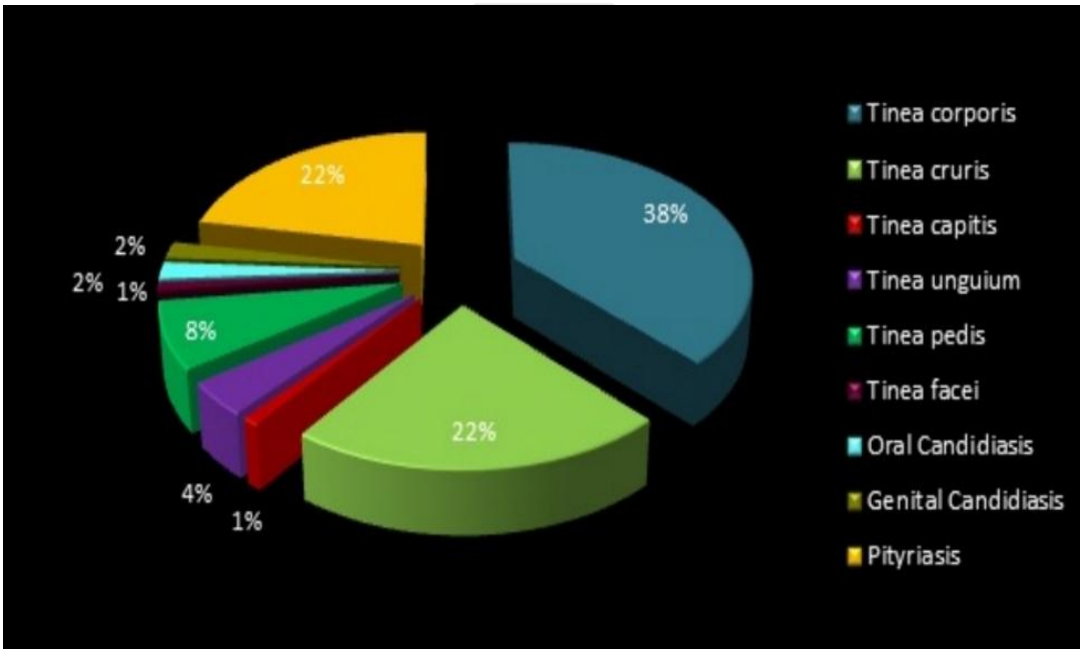

Figure No. 3: PREVALENCE OF FUNGAL INFECTIONS [27]

STUDY DESIGN

The following group of studies was a prospective, randomized, open labeled, parallel group study to assess the therapeutic responses to certain topical antifungals. Clinically diagnosed healthy adult patients with **tinea corporis, tinea cruris,** and **tinea pedis** requiring topical antifungal therapy were selected for the study. A detailed history including the duration of disease, associated medical condition, the treatment history, and family history was taken. The patients above the age of 18 with clinical evidence of cutaneous mycoses were clinically evaluated.

KOH microscopy has been done to evaluate the results. [28,29]

Inclusion Criteria

- Patients of either gender over 18 years of age.
- Patients with a mycological diagnosis of tinea corporis / tinea cruris confirmed by microscopic KOH wet mount.
- All patients with symptoms of cutaneous mycoses with the target site characterized by at least 2 of the 3 major symptoms.[30]

Exclusion Criteria

- Pregnant and lactating females.
- All other clinical types of tinea infections.
- Patients with HIV / AIDS disease.
- Patients with a history of intolerance or hypersensitivity to the imidazole compound.
- Patients with a known history or clinical evidence of severe cardiac, pulmonary, gastrointestinal, renal, hepatic, or neurological disease, and uncontrolled Diabetes Mellitus. [30]

Drug administration

Patients were randomly assigned to receive topical treatment of luliconazole and terbinafine.

STUDY CASE 1

According to study, the comparative assessment of 1% Luliconazole and 1% Terbinafine results have been recorded taking into consideration the different parameters including the signs and symptoms, KOH microscopy, and duration of the lesion at the time of presentation. And the study was conducted on 60 patients. The study was conducted on a group of 30 patients for Luliconazole treatment and a group of 30 patients for Terbinafine treatment.

In the luliconazole group, 15 patients were of tinea cruris and 15 patients were of tinea corporis.

In the terbinafine group, 19 patients were of tinea cruris and 11 patients were of tinea corporis.

Terbinafine group: About 80% of patients presented with a diameter of 4×5 cm as the size of the lesion, the remaining 20% of patients had a diameter ranging from 2×2cm to 7×8 cm.

Luliconazole group: About 40% of patients presented with a diameter of 4 ×4 cm as the size of the lesion; the remaining 60% of patients had a diameter ranging from 2× 1cm to 5× 5cm.

Types of the lesion in both the groups were scaly and erythematous. A complete cure was observed with both the drugs by the 15th day. None of the patients reported any serious adverse effects during the entire study period in both groups. About four patients, in the terbinafine group, showed mild contact dermatitis, which wasn't a troublesome issue for their entire treatment & follow up period. No incidence of contact dermatitis was noticed among patients of the luliconazole group. [31]

None of the patients in this study had a history of tinea corporis/tinea cruris. Types of the lesion in both the groups were scaly & erythematous. [32]

About 36.7 % of patients were of tinea corporis & 63.3 % tinea cruris in the terbinafine group and 50% were of tinea corporis & 50 % of tinea cruris in the luliconazole group. This shows that the percentage of patients presenting with tinea cruris seems to be more than 50% in both the drug group. [33]

Two weeks of treatment with terbinafine and luliconazole has shown to cure tinea corporis and cruris infection

Twice a day treatment for 14 days with terbinafine was found to be effective in tinea cruris, with a mycological cure rate of 78% at the end of therapy and 89 % at the end of 4th week, as compared to 100% at the end of therapy and no cases of relapse at the 4th week. [33]

Two week treatment with 1% luliconazole cream is effective in treating mild tinea corporis and cruris infection and its efficacy is comparable to 1% terbinafine.[34]

Table 1.1- Demographicdetail [35]

	1% terbinafine group (n=30)	**1% luliconazole group (n=30)**
Age (years)	33.80±9.58	33.90±9.58
12 - 40	24	29
41 - 60	6	1
Males	19 (63.3%)	16 (53.3%)
Females	11 (36.3%)	14 (46.7%)

Table 1.2 – Duration of lesion at the time of presentation [35]

Duration (days)	**No of patients of 1% Terbinafine group**	**No of patients of 1% Luliconazole group**
3 - 10	12	5
11 - 20	12	20
21 - 31	6	5

Table 1.3 – Response to treatment in both group [35]

Group	**Tinea corporis (%)**	**Tinea cruris (%)**
Luliconazole 1%	15(50)	15(50)
Terbinafine 1%	11(36.7)	19(63.3)

STUDY CASE 2

According to study, the comparative assessment of 1% Luliconazole and 1% Terbinafine results have been recorded taking into consideration different parameters including the signs and symptoms and KOH microscopy.

Patients who have fulfilled the selection criteria were randomized into 2 groups as Group A (1% Terbinafine) and Group B (1% LLCZ) applied once daily for two weeks. A total of 120 patients were involved in this study. In this 113 patients were completed the study and 7 patients were dropped out of the study.[36]

The results indicated that one week of treatment with 1% LLCZ is sufficient in the case of tinea corporis and tinea cruris infection. It is inferred that high effectiveness is seen with a shorter duration of therapy with 1% LLCZ.[37]

The results indicated that the 1% LLCZ cream is sufficiently effective for short term therapy than Terbinafine in treating Tinea corporis and Tinea cruris. There were no serious adverse events observed in the study period.[38]

The majority of the patients (72%) receiving 1% LLCZ cream achieved resolution of symptoms within the first week of therapy than the terbinafine group (59%). The reduction in symptoms was higher (91%) in the 1% LLCZ cream group at the end of 2nd week also.[39] LLCZ is capable of producing marked improvement in clinical signs and symptoms as well as eradicating the fungi effectively and this effect is evident in half of the treatment time required for 1% terbinafine.[40]

Hence topical 1% LLCZ cream seems to be a promising medication in treating tinea corporis & tinea cruris in its better therapeutic efficacy as well as safety aspects than 1% terbinafine cream.[41]

Table 2.1 – Demographic detail [42]

	1% terbinafine group (n=60)	1% luliconazole group (n=60)
Age (years)		
Up to 20 years	8 (14.3%)	6 (10.5%)
21-30 years	18 (32.1%)	19 (33.3%)
31-40 years	19 (33.9%)	14 (24.6%)
41-50 years	5 (8.9%)	8 (14.0%)
Above 50 years	6 (10.7%)	10 (17.5%)

Table 2.2 – Duration of lesion at the time of presentation [42]

Duration (Weeks)	No of patients of 1% Terbinafine group	No of patients of 1% Luliconazole group
< 2 weeks	12	10
2-3 weeks	41	42
>3 weeks	3	6

Table 2.3 – Response to treatment in both group [42]

	1% Terbinafine	1% Luliconazole
1st week	59%	72%
2nd week	86%	91%

CONCLUSION

In both the studies (Case study 1 and Case study 2) it has been observed that the Two-week treatment with terbinafine 1% cream & luliconazole 1% cream achieved a 100% conversion rate (positive KOH mount microscopy to normal microscopy), with lesser number patients in both the groups. Luliconazole is the newer topical azole which has fungistatic action as

compared to terbinafine's fungicidal effect. So the equal efficacy of luliconazole has dermatophytoses especially pruritus thereby improving patient's quality of life. Hence, for two weeks, once a day application of terbinafine & luliconazole were equally effective for the treatment of tinea corporis/cruris infection. Also topical 1% Luliconazole cream seems to be a promising medication in treating tinea corporis & tinea cruris due to its better therapeutic efficacy as well as safety aspects than 1% terbinafine cream.

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