"CLINICAL EFFICACY OF TOPICAL TERBINAFINE VERSUS TOPICAL LULICONAZOLE IN TREATMENT OF TINEA CORPORIS/TINEA CRURIS PATIENTS"

BY

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IN

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Dr.GIRISH.M.BENGALORKAR, M.D

DEPARTMENT OF PHARMACOLOGY
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Sri Devaraj Urs Academy of Higher Education and Research

Tamaka, Kolar, Karnataka

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I hereby declare that this dissertation entitled **"CLINICAL EFFICACY OF TOPICAL TERBINAFINE VERSUS TOPICAL LULICONAZOLE IN TREATMENT OF TINEA CORPORIS / TINEA CRURIS PATIENTS "** is a bonafide and genuine research work carried out by me under the guidance of **Dr.GIRISH.M.BENGALORKAR**, Associate Professor, Department of Pharmacology.

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This is to certify, the ethical committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved, ***Dr.Vidhya Lakshmi C.P,*** Post Graduate student in the department of Pharmacology at Sri Devaraj Urs Medical College, Kolar to take up the dissertation work titled ***"Clinical efficacy of topical terbinafine versus topical luliconazole in treatment of tinea corporis/tinea cruris patients"*** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, Karnataka.

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DEDICATED WITH REVERENCE
TO

MY

PARENTS

WHOSE SELFLESSNESS AND INSPIRATION

MOTIVATES ME IN ALL MY ENDAVEOURS

ABSTRACT

Background/objectives:

Tinea infections (tinea corporis &t tinea cruris) of skin respond well to topical antifungal therapy, but the need to apply cream 2- 3 times daily for up to 4 weeks can impair compliance & lead to treatment failure. Luliconazole is one of those drugs offering good efficacy & tolerability with a short duration of treatment. Terbinafine, an allylamine antifungal agent, 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 are lack of studies between terbinafine & luliconazole, the present study was undertaken to compare the clinical efficacy in tinea corporis/tinea cruris patients.

MATERIAL & METHODS:

Study was conducted on 60 patients presenting to Dermatology out patient department of Sri R. L Jalapa Hospital, Kolar, from 1st December 2010 to 30th April 2012. Patients alternatively assigned to either terbinafine or luliconazole & advised to apply test drugs topically for 14 days. Clinical symptoms & signs were assessed using 4-point (pruritus, erythema, scaling) scale & 10% KOH mount at base line, end of treatment visit (15th day) & later 30th day. The data was analysed based on age, gender distribution, duration of lesion, clinical score & KOH mount.

RESULTS:

Of the 60 patients recruited, all came for 1st follow up (14th day)& 51 patients for 2nd follow-up (30th day).The male to female ratio was 1.75:1.15 in both the groups, mean age of the patients was 33.80± 9.58 years in terbinafine & 33.90 ± 9.58 years in luliconazole group. Maximum number of patients was in 12- 40 years aged in both group. Sixty patients and 51 patients were negative for KOH mount preparation on 15th & 30th day respectively. At the end of first follow-up, the clinical score was reduced from 3 to zero (P=0.0001) in both the treatment groups. Mycological cure was 100% in both the drug groups. There was no relapse in 51 patients who came for 2nd follow-up. Four in terbinafine and 5 in luliconazole group were lost to follow-up.

CONCLUSION:

1. Only mild forms of tinea infections were included when compared to other studies where moderate to severe (pustules, incrustations, vesiculation) were included. Hence the onset of illness, treatment duration and severity of illness were in favour in our study for 2 weeks.

2. In both the treatment arms, clinical & mycological cure was comparable, hence two weeks once a day application of terbinafine & luliconazole were equally effective for treatment of tinea corporis/cruris infection.

Key words:

Topical terbinafine 1% cream, topical luliconazole 1% cream

Tinea corporis, tinea cruris

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INTRODUCTION

Superficial fungal infections of skin caused by dermatophytes constitute an important public health problem.[1,2] Tinea corporis and tinea cruris are commonly seen in day to day outpatient basis in Dermatology centers throughout the world and an important clinical problem that may at times be a therapeutic challenge.[3] The broad spectrum topical antifungal drugs like imidazole (clotrimazole and miconazole) or the newest class, the allylamines (Ex: naftifine and terbinafine) have been shown in comparative studies to produce higher cure rates and rapid responses.[4] In addition, sertaconazole has also shown superior activity and efficacy in treatment of superficial fungal infections as compared to fluconazole, clotrimazole, bifonazole and others, however once again with the limitation of fungistatic activity against dermatophytes.[5]

With a continuous search for a drug that has preferable biological features as a potent topical antifungal drug and efficacious with minimal dosing of once daily and the mechanism of action that overcomes host resistance, having short period of recovery and with the hope of improving patient compliance was researched.[6] This research resulted in discovery of a member of imidazole group, optically active (R) – Enantiomer fungicidal azole named “LULICONAZOLE”, in 2005.

Since no study is available comparing the efficacy of topical terbinafine versus topical luliconazole in the literature on Indian rural population, the present study has been taken up**.**

AIMS and OBJECTIVES

- To study the clinical efficacy of topical luliconazole on tinea corporis / tinea cruris patients.
- To compare the clinical efficacy between topical terbinafine and topical luliconazole on tinea corporis / tinea cruris patients.

REVIEW OF LITERATURE

FUNGAL INFECTION

Fungi affect humans in a number of ways. They can destroy crops, there by promoting starvation in tropical areas: some fungi such as mushrooms are poisonous, act as allergens, producing asthma and hypersensitivity pneumonitis and some are invasive. The latter may be subdivided into those invading the skin, subcutaneous tissues and deep tissues.

Superficial infections of skin include thrush and the ringworm. Subcutaneous infections are usually topical in distribution, e.g. mycetoma. Deep fungal infection is often opportunistic, occurring in immuno-compromised individuals e.g. cryptococcus-affecting lungs.[7] Fungal infections of skin are commonly known as 'ringworm'. Fungi consist of thread like hyphae, which form tangled masses, or mycelia, in the common moulds. In "Dermatophyte" fungal infection of skin and nails, these hyphae invade keratin and are seen as microscopic examination of keratin from infected tissues. When the immune response is impaired, superficial infection may invade the deeper tissues.[8] Tinea or ringworm is a group name for a highly contagious, segmental mycelia fungus. It is commonest, single fungus group of infections found in tropical countries. There are three distinct genera in the group (distinguished by cultural characteristics). Epidermophyton: affects only human skin, important species is, E. floccosum, Trichophyton: more virulent than others, affects hair, the glabrous skin, as well as nails. It includes both human and animal species; important species are T.rubrum, T.mentagrophyte, T.violaceum and T.schoenleine. Microsporum: affects mainly hair, less commonly glabrous skin, important species are M. audounii and M.canis and lanosum.[9]

Superficial fungal infections of skin caused by dermatophytes constitute an important public health problem of which, tinea corporis and tinea cruris is commonly seen in day to day outpatient basis in Dermatology centres throughout the world and an important clinical problem that may at times be a therapeutic challenge.

TINEA CORPORIS

Definition:

Ringworm of glabrous skin.

By definition it includes lesions of the trunk and limbs excluding ringworm of specialised sites such as scalp, feet and groins etc.[10,11,12]

Aetiology:

All species of dermatophyte belonging to genera Trichophyton, Microsporum, or Epidermophyton are capable of producing tinea corporis, most common causative organisms are T.rubrum, M.canis and T.mentagrophytes.[13]

Epidemiology:

The organism responsible for tinea corporis may be transmitted by direct contact with other infected individuals or by infected animals. Its also transmitted from inanimate fomites such as clothing and furniture.[14] A tropical or subtropical climate is associated with more frequent and severe tinea corporis.[15] Children appear to have increased incidence of tinea corporis caused by zoophilic organisms. M. canis is transmitted by contact with pets (especially cats and dogs), Tinea imbricate, caused by T. concentricum, is geographically limited to certain areas of Far East, South Pacific, and South and Central America, like favus, tinea imbricate is probably contracted in early childhood and can persist for a lifetime.[16]

Pathogenesis:

The causative organism of tinea corporis generally reside superficially in stratum corneum, hair follicle involvement can occur- especially with T.rubrum or T.verrucosum and seems to be associated with increased inflammation, the pathogenic sequence of events are as follows: The first step involves invasion of stratum corneum, possibly with help of warm, moist occlusive conditions.[17] After a 1 to 3 week incubation period, centrifugal spread occurs. The active advancing border of infection has a increased epidermal turnover rate.[18] Presumably, the host epidermis is attempting to shed the organism by increasing epidermal turnover to exceed the fungal growth .Temporary resistance to re-infection occurs in this area for a variable time, however, second waves of infection are commonly seen later.[19,17]

Clinical features:

The most common presentation is the typical annular lesion with an active, erythematous and sometimes vesicular border.

Special forms and species variations:

Lesions of glabrous skin due to M.canis are not rare, they are as common in both adults and children and are characteristically annular.[20] T. equinum from horses also gives plaques of tinea corporis. T.verrucosum from cattle, T. erinacei from hedgehogs, T. mentagrophytes from small rodents in general and M. persicolor from wholes are all likely to cause inflammatory lesions of exposed skin. T. verrucosum can lead to extensive annular lesion of the upper trunk, especially in children.[21]

T. rubrum may invade the buttocks and lower back as well as more distant sites of the trunk as extension from tinea cruris. On the legs and usually extending from feet T.rubrum may cause typical lesions with raised margins, but rather psoriasiform

lichenified plaques without central clearing may also occur and a variety of vasculitis like lesions are recognised. The perifollicular granulomatous papules of the Majocchi type are classical but Bazin-like plaques sometimes occur with an almost haemorrhagic appearance.[17,22] T.schoenleinii produces characteristic crusted lesions on the glabrous skin closely resembling scalp changes of favus. Tinea imbricate caused by T. concentricum affects both the gender of all ages. The infection begins as brownish scaling, centrifugal spread follows, but within the area of central clearing a second wave of scaling soon arises. Pruritus is intense and may lead to lichenification.[23]

Atypical deep forms of tinea corporis: In very little rare number of patients, depression of cellular immune responses is associated with the presence of a serum factor, possibly circulating antigen. Such cases may present with dermal nodules, abscesses or draining sinuses.[24,25]

INVESTIGATIONS

Laboratory studies

Microscopic examination of KOH wet mount of scales is diagnostic of tinea corporis and tinea cruris. The procedure is discussed in material & methods.

Growth on Mycoses or Sabouraud agar plates usually is sufficient within 3-4 weeks to allow specific fungal identification.[26]

Laboratory findings

Specimens for KOH examination should be obtained from actively spreading border of lesion, where organisms are more numerous and the chances of a positive examination are higher. There are septate, branching hyphae in the stratum corneum.

Pathology

Histopathologically, fungal organisms can be seen in the stratum corneum in the usual case of tinea corporis. With haematoxylin and eosin, they appear basophilic, with PAS, the fungal elements stain red, with silver methylamine, they stain black. If vesiculation is present, it's seen as spongiotic vesicle. In the nodular perifolliculitis variant caused by T. rubrum, there is a perifollicular granulomatous reaction, often associated with central necrosis and suppuration.[27]

DIFFERENTIAL DIAGNOSIS

In usual annular ringworm infection, entities such an erythema annulare centrifugum, nummular eczema and granuloma annulare should be considered.

Erythema annulare centrifugum generally shows scaling at the tailing edge of the advancing border, whereas tinea corporis shows scaling over the entire advancing edge.

In nummular eczema, lesions show eczematous change or crusting throughout the entire lesion, no central clearing is seen. Furthermore, lesion tend to be more numerous and symmetric than in tinea corporis.

In granuloma annulare, intradermal papules without significant epidermal change make up the border of the lesions.

If the clinical lesion is more papulosquamous in appearance, other typically papulosquamous entities can be considered (i.e. psoriasis, lichen planus, secondary syphilis, seborrhoeaic dermatitis, pityriasis rosacea).

Tinea faciei may resemble lupus erythematous or dermatomyositis. Other entities to be considered include photodermatoses such as polymorphous light eruption, contact dermatitis or acne rosacea.

TREATMENT

For isolated lesions of tinea corporis, topical agents such as allylamines (naftifine, butenafine & terbinafine), imidazole (miconazole, econazole, oxiconazole, sertaconazole) can be used. For widespread lesions, griseofulvin is used in a dose equivalent to 1g/day of the micronized drug.

A recent study showed that a single 200mg dose of fluconazole is effective even in tropical environments where there is higher incidence of tinea corporis.[28]

TINEA CRURIS

Definition:

Tinea cruris also known as **crotch itch, crotch rot, eczema marginatum, gym itch jock itch and ringworm of groin** in American English and **dhobi itch or scrot rot** in British English is a dermatophyte fungal infection of groin region in either gender.[29]

Tinea cruris is a sub acute/chronic dermatophytosis of groin, pubic regions and thigh.

Epidemiology and Aetiology

Age of onset: teen and young adults

Gender: males > females, also common in teen females who are overweight/wear occlusive clothing.

Aetiology: E. floccosum, T. rubrum, T.mentagrophyte are commonest organisms.

Predisposing factor: Warm, humid environment, tight clothing worn by gender, obesity, chronic topical glucocorticoid application, those with weakened immune system (HIV /immunosuppressant drugs), & those who are closely associated with animals & contact sports (wrestling, soccer).

Duration: months to years, often a history of longstanding tinea pedis and prior tinea cruris is present.[30]

Pathogenesis:

Often associated with tinea pedis.

Groin inoculated with patients hands.

Clinical features:

Symptoms: Pruritus is a common symptom.

Signs:

1. Distribution: bilateral thighs, inguinal folds, buttocks.

2. Spared areas: Scrotum and penis, if involved suspect cutaneous candidiasis.

3. Characteristics: Asymmetric erythematous annular plaques, scaling, central clearing, occasional papules/vesicles.[31]

These infections are generally worse during summer and rainy season and tend to heal spontaneously during winter. Patients with immuno- compromised tend to have wide spread infections[32], fortunately tinea cruris is not contagious. The patients own case of athlete foot is usual source of infection and re-infection of groin.[33]

An well defined itchy red scaling patches occur asymmetrically in medial aspect of .both groins, extending down the thigh and in scrotum unless treated,[34] lesions start at apex of groin and extend to inner aspect of thighs, genitalia, perineum or gluteal region.[35]

Central clearance is usually present, occurs in adults wearing clothes made up of synthetic material such as terylene and nylon which tend to accumulate heat and humidity in skin,[36] large patches of erythema with central clearing are centred on inguinal creases and extend distally down the medial aspect of thigh and proximally to lower abdomen and pubic area.

In acute infection, rash may be moist and exudative. Chronic infection typically are dry with papular annular, aciform border and barely perceptible scale at margin,

central areas typically are hyperpigmented and contain a scattering of erythematous papules and a little scaly lesion.

Secondary changes of excoriation, lichenification and impetiginisation may be present as result of pruritus. Chronic infections modified by application of topical corticosteroid are more erythematous, less scaly and may have follicular pustules. Approximately one half of patients with tinea cruris have co-existing tinea pedis.[37]

INVESTIGATIONS

The microscopic examination of KOH wet mount and histological findings are identical to those described with tinea corporis.

PROPHYLAXIS [38]

1. Patients who sweat a lot should change their clothes frequently, wear cotton socks and avoid synthetic materials

2. Advised to use clothes, especially underwear and towel to be boiled in hot water

3. Advised to use footwear of open type, permitting sufficient aeration

4. Advised to keep their intertrigeninous areas dry with powder especially talcum or antifungal powder

5. Advised to use their own towel

6. Advised to dry their groin after bathing

7. Over weight people are advised to lose their weight, to reduce chafing and sweating

8. Advised to put on dry clothes right away immediately after swimming

DIFFERENTIAL DIAGNOSIS

The crural region may be infected by other dermatosis that presents comparable clinical features as tinea cruris.

Psoriasis, seborrhoeaic dermatitis, candidiasis, erythrasma, lichen simplex chronicus, Dariers disease and pemphigus vegetans may be mistaken for tinea cruris. [39]

Candidiasis – usually seen more often in females and doesn`t seem to have characteristic raised beaded margin, instead has white pustules with numerous and small satellite lesions, with a frayed peeling edge that occurs as tiny pustules rupture.

Pityriasis versicolor and erythrasma are usually non-inflammatory and asymptomatic and rarely has any central clearing.

Intertrigo with heavy bacterial colonization is especially seen in obese people, where there may be a sharp margin, but is usually a simple curve where the opposed skin surfaces meet.

Psoriasis and mycosis fungoids may occasionally mimic tinea cruris, but characteristic lesions in other sites can usually be found.

In atopic eczema, there may be lichenification, but these changes usually extend towards hip.

TREATMENT

It is often treated with antifungal drugs applied topically. Traditionally creams containing tolnaftate, ciclopirox, terbinafine, econazole nitrate, oxiconazole, naftifine, clotrimazole, miconazole have been used.

If skin inflammation causes discomfort and itching, glucocorticoid (such as 1% hydrocortisone cream) may be combined with antifungal drug to help prevent further irritation due to patient scratching in the area. Apart from quicker relief of symptom, this also helps minimize risk of secondary bacterial infection caused by scratching. However steroids may exacerbate the condition, if used alone for fungal infections because they hinder the body immune system.[39]

TERBINAFINE

Introduction:

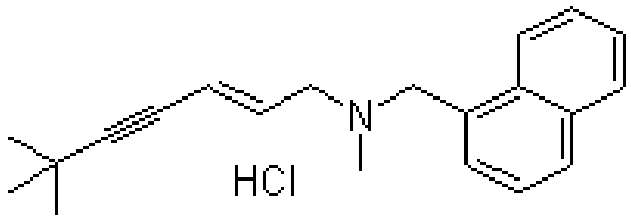
Discovered in 1983, terbinafine is a member of allylamine class of antifungal. It differs from the parent compound, naftifine, by the presence of a tert-butyl acetylene substitution of the phenyl ring on the side chain of the molecule. This substitution confers an increase in oral efficacy and an additional 10 to 100 times in vitro activity of naftifine.[40,41]

Formulations available are: terbinafine hydrochloride 1% cream, 1% gel, film forming solution.

PHARMACODYNAMIC PROPERTIES

CHEMICAL STRUCTURE: Chemically is (E) - N-(6, 6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine monohyrochloride.

US, FDA approved the first generic version of prescription Lamisil (terbinafine hydrochloride) tablet.



MECHANISM OF ACTION AND SPECTRUM:

It inhibits fungal growth by disrupting sterol biosynthesis ,abrogates the formation of ergosterol by inhibiting squalene epoxidase, the catalytic enzyme responsible for converting squalene to 2,3-oxidosqualene (an ergosterol precursor),resulting in deficiency of ergosterol ,compromising cell wall integrity &contributes to impaired growth /death of the pathogen.[42,43]In vitro,the minimum concentration of terbinafine required to inhibit 95% of squalene epoxidase (IC_{95}) is 2 to 3 orders of magnitude greater for the mammalian enzyme (300μM) than for enzymes isolated from pathogenic yeast (0.6-2.1μM).[5] Hence human toxicity is less.

Greatest activity against species within the Trichophyton mentagrophytes & rubrum, Epidermophyton floccosum, followed by dematiaceae, Candida albicans respectively.[45,46,47] The MICs reported for terbinafine against various dermatophytes are typically comparable to or lower than those of other antifungal active against these organisms, namely triazoles, imidazole & griseofulvin.[48]

The increase in resistance to azoles antifungal observed with the arthroconidia of the dermatophytes has not been observed with terbinafine. Both arthroconidia & microconidia of selected trichophyton species demonstrate the same susceptibility profile to terbinafine in vitro[49], the significant clinical relevance is the activity of terbinafine when used in combination with other antifungal for management of invasive mycoses. Against Aspergillus fumigatus, indifference is primarily observed when its combined with Amphotrecin B .Similarly it doesn't improve the activity fluconazole or itraconazole against A.fumigatus, however triazoles demonstrates synergism when added to terbinafine.[50] Those yeast organisms which are resistant to fluconazole , shows synergism with fluconazole and itraconazole , of which Candida

glabrata >Candida tropicalis > Candida kreusi.[51] Against ocular isolates of Fusarium, the combination of Amphotrecin B & terbinafine was synergistic.[52]

PHARMACOKINETIC PROPERTIES:

ABSORPTION and BIOAVALABILITY

Is efficiently absorbed following oral administration (BA approx. 70%).[53] At clinically relevant doses (125-750mg), it demonstrates a linear absorption profile with total body exposure increasing in direct proportion to dose.[54]

The rate of absorption does not appear to differ substantially between children & adults, however extent of absorption as reflected by maximum plasma concentrations is markedly lower in children when doses are normalized per kilogram of body weight.[55]Following topical administration to normal skin, cream & gel –based terbinafine formulations attain concentration ranging from 746 to 949ng/$cm^{2.}$.

Maximum stratum corneum concentrations increases by 15% with 7 days of application, however the area under the plasma concentration versus time curve (AUC) increase by as much as 40% over 1 week. While topical preparations are well absorbed into the stratum corneum ,the resultant systemic exposure is lower than those observed with after oral terbinafine administration.[56]

DISTRIBUTION:

Extensively distributed with estimates of apparent distribution volume approaching 20 L/kg.[57] This relatively large volume of distribution results from the drugs high degree of lipophilicity, extensive protein binding profile & ability to concentrate in adipose & keratin rich tissue.[58] At steady-state concentrations observed in sebum ,stratum corneum & hair exceeds those observed in the plasma. Terbinafine

concentrations remain elevated following discontinuation of oral therapy & persist in excess of 1 month after stopping treatment.[59]

New formulation - Polymeric film forming solution designed as a one-time dose. The acrylate/cellulose/triglyceride based formulation leaves a nearly invisible, highly concentrated film on the skin after the carrier solvent (ethanol) has evaporated. This film remains on the site of infection nearly 6 times longer than other topical preparations & results in stratum corneum concentrations that are sustained above the MIC in excess of 2 weeks after application.[60,61] After oral administration ,terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1.

METABOLISM:

At least 7 cytochromes P450 (CYP) appear to be responsible for metabolizing terbinafine into more than 15 metabolites.[62] In adults, the N-demethyl & caboxybutyl metabolites constitute the largest fraction of the metabolites observed. Although the metabolites lack an appreciable antifungal activity, they may contribute to the drug interactions & /or side effects observed following administration.[63] Because of the the polyfunctional nature of terbinafine as a substrate for CYP450, the magnitude of potential drug interactions would be predicted to be low as compared with other drugs.[64,65] It exhibits potent inhibition of CYP2D6 in vitro & correspondingly marked reduction in the metabolism of CYP2D6 substrate dextromethorphan in vivo.[66] Clinically, terbinafine is demonstrated to interact with concurrently administered CYP2D6 substrates including amitriptyline, nortriptyline, desipramine & venalafaxine.[67,68,69]

Other drugs which tend to interact with terbinafine include perphenazine, metoprolol and propafenone.[70]

ELIMINATION:

Clearance is triphasic with the terminal elimination half life approximating 100 hrs after a single dose & 22 days with duration of therapy spanning several months.[71] Approximately 80% of terbinafine metabolites are excreted by the kidney with the remaining fraction eliminated in the faeces.[72] This rate of elimination accounts for the magnitude of accumulation observed with terbinafine after repeated dosing & the persistence in plasma & tissues long after discontinuation of the drug. While this confers a distinct advantage to the allylamine permitting shorter courses of therapy.[73]

THERAPEUTIC USES

1. Tinea corporis

2. Tinea cruris

3. Tinea pedis

4. Tinea capitis

5. Onychomycosis

6. Tinea versicolor

DOSAGE and ADMINISTRATION

1. DOSAGE:

DOSAGE: - Oral

Paediatric patients – for tinea capitis

Some evidence that a longer duration of treatment (e.g., 6-8 weeks) may be necessary when tinea capitis is caused by M.canis.[74,75]

Adults – for Onychomycosis

Fingernails:

Tablets: 250mg daily given for 6 weeks. More prolonged treatment has not been more effective,[76] although some patients may benefit from extended and / or repeated courses of terbinafine.[76,77]

Fingernail infections usually are re-evaluated ≥ 18weeks after completion of treatment.[78]

Toenails:

Tablets: 250mg daily given for 12weeks. Some patients who do not respond to the initial 12-week regimen may respond to a second course.[76,79]

Toenail infections usually are re-evaluated 6-9 months after completion of therapy.[79]

Tinea corporis ± or tinea cruris

Tablets: 250mg daily for 2-4weeks has been used.[80]

DOSAGE: Topical

Paediatric patients:-for tinea corporis or tinea cruris

Tinea corporis or Tinea cruris:

Children ≥ 12 years of age: apply cream once or twice daily for ≥ 1week.[81,82]

Tinea Pedis:

Children ≥ 12years of age: apply 1% cream or film forming solution twice daily (morning and evening) for ≥ 1week.[83,84]

Adults:- tinea corporis or tinea cruris and tinea pedis

Tinea corporis or Tinea cruris:

Apply cream once or twice daily for ≥ 1 week.[85,86,81,82]

Tinea Pedis:

Apply cream or film forming solution twice daily (morning and evening) for ≥ 1 week.[87,88,82]

1. ADMINISTRATION:

Apply a sufficient amount of 1%cream or film forming solution either once or twice daily; rub gently into affected area and surrounding skin.[85,87,82]

General precautions:

Clinical improvement usually is evident within first week of therapy, and patients treated for 1-2 weeks usually show continued improvement for several weeks after completion of treatment.[85,86,81]

Selection and use of antifungal for Onychomycosis:

When selecting an antifungal for treatment of Onychomycosis, consider reported adverse effects and risk of serious effects, need for prolonged therapy, cost and risk of relapse.[84] Toenail infections generally require more prolonged antifungal therapy than fingernail infections.[76,77,78,79] The optimal clinical effect of terbinafine in treatment of Onychomycosis is not seen until several months after mycological cure and

completion of treatment, and is related to the period required for outgrowth of healthy nail.[78,79]

Precautions:

Hepatotoxicity:

Hepatotoxicity, including abnormal liver function tests and severe cholestatic hepatitis, reported in some patients receiving oral terbinafine.[89,90,91]

Liver failure, sometimes leading to death or liver transplant, occurs rarely in patients with or without pre-existing liver disease receiving oral terbinafine for treatment of onychomycosis.[90,91]

Dermatologic effects:

Psoriasiform eruptions or exacerbation of psoriasis and acute, generalized exanthematous pustulosis reported.[92]

SPECIFIC POPULATIONS:

Hepatic impairment:

Clearance may be decreased substantially (about 50%) in adults with hepatic cirrhosis.[85]

Not recommended in patients with active or chronic liver disease.[93]

Renal impairment:

Clearance may be decreased substantially (about 50%) in adults with renal impairment ($Cl_{cr} \leq$ 50 ml/minute).[85]

There are not enough studies present, which supports the above line.[93]

ADVERSE EFFECTS:

Mild or moderate includes :diarrhoea ,dyspepsia, nausea, vomiting, abdominal pain, taste disturbances, headache , fever , upper respiratory tract infection or symptoms (cough, nasopharyngitis, nasal congestion , pharyngolaryngeal pain , influenza).[94] Serious adverse reaction ranging from hepatotoxicity to fulminant liver failure, onset typically occurs after 3weeks of therapy & resolution can take as long as 3 months after discontinuation of the drug. Others which are rare are blood dyscrasias including leucopoenia, agranulocytosis, neutropenia & pancytopenia, most cases occur between 4 to 5 weeks of therapy & resolve within a week after stopping the medication.[22 Severe] Dermatologic eruptions including TEN, acute generalized exanthematous pustulosis & SJS (Steven's Johnson syndrome) are also reported.[96] Possible risk factors for developing terbinafine associated taste loss include an age > 65yrs & BMI < 21 $kg/m^{2.}$.[97] Ocular side effects like bilateral anterior optic neuropathy with decreased vision and optic disc oedema was reported in a patient 2 weeks after starting terbinafine (500mg/day).[98]

DRUG INTERACTIONS:

Co administration with drugs predominantly metabolized by CYP450 2D6 isomenzyme (tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers) should be done with careful monitoring & may require a reduction in dose of the 2D6- metabolized drug. In vitro studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin & cyclosporine. It decreases the clearance of caffeine by 19% and increases the clearance of cyclosporine by 15 % respectively. It either increases or decreases prothrombin times in patients concomitantly taking oral terbinafine &

warfrain. Terbinafine clearance is increased 100% by rifampin, a CYP450 enzyme inducer, & decreased 33 % by cimetidine, a CYP450 enzyme inhibitor. Terbinafine clearance is unaffected by cyclosporine.

CONTRAINDICATIONS:

In individuals with hypersensitivity to terbinafine or to any other ingredients of the formulation.

Pregnancy & lactation as they get actively secreted in the breast milk.[99,27]

LULICONAZOLE

Introduction:

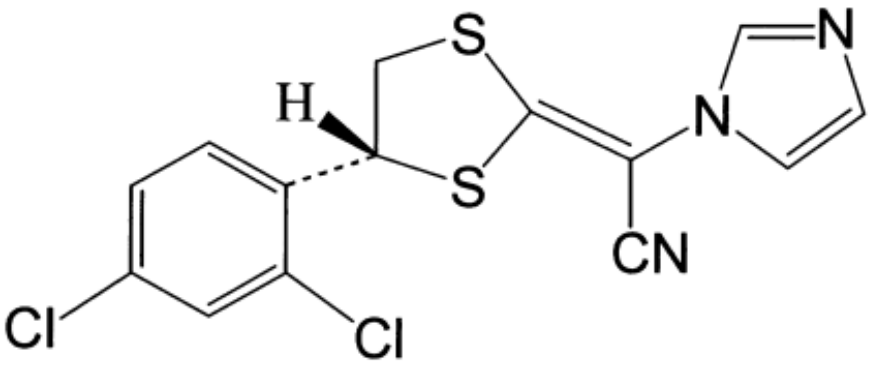
Broad-spectrum antifungal agents act by blocking specific steps in the synthesis of fungal cell membrane components .The broad spectrum topical antifungal drugs like imidazole (e.g. Clotrimazole & miconazole), or the newest class, the allylamines (eg.naftifine & terbinafine) have been shown in comparative studies to produce higher cure rates & rapid responses, with limitations of action to certain fungi only. For instance the fungicidal action of terbinafine is only to dermatophyte infections & not against yeast.[100] In addition; sertaconazole has also shown superior activity & efficacy in the treatment of superficial fungal infections as compared to fluconazole, clotrimazole, bifonazole and others, but fungistatic activity against dermatohytes.[101]

As a key approach for increasing the effectiveness of treatment, development of a drug that exerts good efficacy after short period treatment was awaited with a hope of improving the patient compliance and with a preferable biological features as a potent topical antifungal drug & efficacious with minimal dosing of once daily, having short period of recovery would be ideal, which resulted in the discovery of a member of imidazole group, named "LULICONAZOLE", which was approved in 2005.[102]

Formulation available: Topical 1% cream

CHEMICAL STRUCTURE: chemically is 2, 4 –dichlorophenyl of luliconazole structure {(-) – (E) – [(4R) -4-(2,4 – dichlorophenyl) -1,3 – dithiolan -2 – ylidene] (1H – imidazole -1 –yl) acetonitrile}.

Luliconazole is optically active compound



The R-LLZ (Lulifin) possesses a wide spectrum of antifungal activity & is very potent against dermatophytes, both in vitro & in vivo. It is 2.5 & 28 times more effective in inhibition of ergosterol biosynthesis than racemic lanoconazole & bifonazole respectively.

The S-LLZ is inactive as an inhibitor 14α – demethylase, indicating that the stereo chemical orientation of the 2, 4-dichlorophenyl group plays an important role in interaction with the enzyme.[103]

PHARMACODYNAMIC PROPERTIES

MECHANISM OF ACTION AND SPECTRUM:

Primarily affects the fungal cell membrane through inhibition of ergosterol biosynthesis. It inhibits cytochrome PASO sterol 14α – demethylase (CYP51p depending on nomenclature), an enzyme that catalyzes the oxidative removal of 14α-methyl group of lanosterol in the ergosterol biosynthetic pathway, resulting in accumulation of 14α- methylated sterols in the cytoplasmic membrane, which disrupts the phospholipids organisation and impair membrane bound enzyme systems such as ATPase and enzymes of the electron transport system, thus arresting fungal cell

growth. CYP51p enzyme binding is accomplished through coordination of the triazoles nitrogen, N3 or imidazole N4 of luliconazole ring with the cytochrome P-450 heme target site, while the remainder of the luliconazole molecule binds to the apoprotein dependant on its structure.

Studies shown that the stereo chemical orientation of 2, 4 –dichlorophenyl of luliconazole structure {(-) – (E) – [(4R) -4-(2, 4 – dichlorophenyl) -1,3 – dithiolan -2 –ylidene] (1H – imidazole -1 –yl) acetonitrile} plays an important role in the interaction with the enzyme. It brings about efficient intracellular drug processing via inhibition of extracellular proteases needed for fungal growth at sub-MICs. It forms a reservoir on the stratum corneum facilitating its release to the infected area effectively.[104]

Active against many fungi, including dermatophytes (Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Microsporum gypsum), filamentous fungi (e.g.Aspergillus fumigatus), dematiaceous fungi (e.g. Fonsecaea pedrosoi, F.compacta, Cladospori umcarrionii, Exophiala jeanselmei, E.spinifera), malassezia species and yeasts. More active than azole antifungals (e.g., lanoconazole, bifonazole) and terbinafine against dermatophytes. Active in vitro against some Candida including C. albicans and C.tropicalis, C.glabarata etc. It is superior to bifonazole, terbinafine and fluconazole against Candida species.[102] Superior to bifonazole and terbinafine against malassezia species (M.furur, M.sympodialis, M.sloffiae).[105]

PHARMACOKINETIC PROPERTIES

ABSORPTION and BIOAVAILABILITY:

When a single dose of 5g of luliconazole was applied to the upper dorsal skin in healthy adult males for 24hrs, low concentration of unchanged luliconazole was observed in the plasma 12-24hrs after application, In addition, when repeated doses of the cream were applied for 7 days, low concentration of the unchanged luliconazole was observed in the plasma 6 hrs after the initial application. The plasma luliconazole concentration ,24hrs after application of cream is about 1.9 times higher after the last application than that at the 1st application, while the concentration remained at an approximately constant level at the 3rd application or later, and plasma luliconazole after repeated application rapidly disappeared. Therefore, repeated application does not seem to cause accumulation.

DISTRIBUTION

A maximum radioactivity concentration was reached in most tissues at 12 hours after single percutaneous administration of 1% cream. Large distribution is observed in the liver and adrenal gland, but the concentrations started to decrease 24 hrs after administration. The changes in the tissue distribution & radioactivity concentrations were similar after repeated administration. Therefore, it is unlikely that this drug gets accumulated or retained in specific tissues.

METABOLISM

A route of metabolism starts with cleavage of the dithiolan ring, leading to various conjugates via thirane, and even isomerisation and cleavage of the imidazole ring in

the early stage of metabolism is assumed on the basis of the analysis of metabolites in urine, bile and in vitro metabolic samples.

A study using human CYP-expressing microsomes showed that CYP2D6 & CYP3A4 were mainly involved in metabolism of luliconazole, & that the metabolites generated by hepatic microsomes were same in rats, dogs and humans. There was almost no metabolism in the skin.

EXCRETION

The urinary & faecal excretion rates after single percutaneous administration of 1% cream in rats were 4.2% & 9.4% respectively & faeces was the main route of excretion, while enterohepatic circulation was also observed. No unchanged drug is detected in the urine.[106]

Dose finding studies

1. In vivo study with guinea pig model of tinea pedis, topical treatment with 0.5% solution of NND502 (luliconazole) was more effective as compared to 0.5% solution of lanoconazole or terbinafine, when administered for 7 days .When the dose was increased to 1 % for all the 3 drug groups, the treatment duration was shortened to 3 days with complete mycological cure in luliconazole group.[107]

2. In a randomised, double blind, comparative study of luliconazole cream of in concentration 1 %(74), 0.5 %(67) & 0.1 %(72 patients) used once daily for 2 weeks in tinea pedis. Mycological cure at the end of 4 weeks was 79.7 %, 76.1% &72.2% respectively.[108]

TOXICITY

The no- observed- adverse-effect level (NOAEL) in general toxicity studies was considered to be 5 mg/kg after 4 week subcutaneous administration,1 mg /kg after 26 week subcutaneous administration and 250 mg/kg after 4 week percutaneous administration in rats.

Several laboratory studies and toxicity data have concluded that no specific or serious toxicity is observed with luliconazole (`1% cream) compared with the existing imidazole topical antimycotic drugs. [106]

PRECLINICAL STUDIES [109]

TABLE: 1 Preclinical studies on luliconazole (in vivo & in vitro)

In vitro	Test drug	Comparator	Outcome
Candida albicans	NND502(luliconazole)	FCZ,ITZ ,AmB	MIC for luliconazole was 1-4 times less than FCZ
Aspergillus fumigates	NND502(Luliconazole)	FCZ, ITZ, AmB	MIC for luliconazole was 60 – 2000 times less than ITZ & AmB

FCZ – fluconazole, ITZ – itraconazole

AmB – Amphotrecin B,

MIC – minimum inhibitory concentration

In vivo study

Orally administration of NND502 (luliconazole) in murine model of systemic fungal infection

	Test drug	Comparator	Outcome
Candida Albicans	NND502 (luliconazole)	FCZ,ITZ	luliconazole was less effective than FCZ,ITZ
Aspergillus Fumigatus	NND502 (luliconazole)	FCZ,ITZ	luliconazole was superior to ITZ & FCZ

FCZ – fluconazole, ITZ – itraconazole

Intravenously administered 2.5mg/kg/day of NND502 (luliconazole) in rat model

Infection	Test drug	Comparator	Outcome
Pulmonary aspergillosis	NND502 (luliconazole)	AmB (5mg/kg/d)	luliconazole was superior to AmB (90% of animals survived in luliconazole group as compared to 30% of AmB)

AmB – Amphotrecin B

THERAPEUTIC USES

1. Tinea corporis

2. Tinea cruris

3. Tinea pedis

4. Cutaneous Mycoses

5. Pityriasis versicolor

Tinea corporis/Tinea cruris/Tinea pedis [110]:

An open label, multicentric, randomised & comparative study comparing the efficacy & safety of luliconazole topical cream (1%) with miconazole topical cream (2%) in treatment of above conditions. The efficacy analysis was based on intent to treat (ITT) population (patients who have at least one post baseline assessment & have achieved at least one dose of the study drug) & per protocol (PP) .The duration of treatment for luliconazole was 2weeks, followed by follow – up period of 2 weeks. The duration of treatment for miconazole was 4 weeks, followed by a follow up period of 2 weeks.

Luliconazole demonstrated significantly better results, than miconazole for key parameters used to assess clinical progression ,with significantly shorter duration of complete resolution of all disease related clinical signs & symptoms (22.3 days vs. 30.6 days, p value < 0.001),time to KOH conversion (12.0 days versus 15.6 days, p value =0.002). For all primary & secondary end points, luliconazole demonstrated therapeutic effect equivalent to or better than that of miconazole in half the treatment period i.e. 2 weeks.

Conversion rate was achieved in 93.5% patients in luliconazole group versus 90.0% in miconazole group. There was no statistically significant difference between the two groups as regards to adverse events, the most commonly reported were pruritus and burning sensation.

TABLE: 2 Efficacy of luliconazole versus miconazole

Primary end points		
Parameters	Luliconazole	Miconazole
Effective treatment	84.9 days	83.9 days
Clinical progress Mycology (time to KOH conversion) days	22.3 days 12.0 days	30.6 days 15.6 days

Secondary end point				
Parameters	Luliconazole		Miconazole	
Effective analysis - Parameter analysis↓	IIT	PP	IIT	PP
Complete cure	60.8	62.9	53.4	57.1
Global clinical Response	99.5		98.2	

IIT – intent to treat, PP- per protocol

Tinea pedis[111]:

In an randomised, double blind, comparative study of luliconazole 1%cream (247 patients) daily for 2 weeks and bifonazole 1% cream(242 patients) for 4 weeks in 489 tinea pedis patients. Clinical improvement was 92% in both groups. Mycological cure at the end of 4 weeks was 76.1% &76% respectively.

Cutaneous Mycoses [106]

Luliconazole susceptibility tests were performed on different fungal strains .The MIC values for luliconazole were compared with those of 3 reference drugs, lanoconazole, bifonazole & terbinafine. Luliconazole inhibited growth of all filamentous fungi at low concentration (MIC $\leq$ 0.004˜~0.125 µg/ml) with the susceptibility of these filamentous fungi almost equal to that to lanoconazole & surpassed bifonazole as well as terbinafine. The yeast like fungi were also susceptible to luliconazole (MIC $\leq$ 0.125 ~ 4µg/ml).

TABLE: 3 Fungicidal activity of luliconazole against C.albicans

MIC against	Luliconazole	Bifonazole	Terbinafine
C.albicans	0.125~4 µg/ml	4~8 mg/ml	>2 µg/ml

Pityriasis versicolor [105]

In vitro study against 3 major Malassezia species, it was established that topical use of luliconazole is equivalent to lanoconazole & inferior to terbinafine (2-3 times), bifonazole (4- 69 times).

DOSAGE and ADMINISTRATION [112]

Luliconazole 1% cream to be applied on the affected area once daily for a period of 2 weeks, followed by a follow up period of 2 weeks.

PRECAUTIONS [112]

For external use only, avoid contact with eyes

Do not apply to the cornea and conjunctiva as ophthalmic use

Do not apply to the areas with marked erosion

SPECIFIC POPULATION [112]

Safety has not been established in pregnancy, lactation and paediatric age group.

ADVERSE EFFECTS

Itching, redness, irritation, contact dermatitis, pain and eczema.[112]

According to the study done by Watanabe S et al, eczema and contact dermatitis (2.6%) was the adverse effects which occurred at site of application, which were mild in severity. [108]

CONTRAINDICATIONS [112]

Contraindicated in patients who have demonstrated hypersensitivity to luliconazole.

MATERIALS AND METHODS:-

Source of data:-

The study was conducted on 60 patients presenting to Dermatology OPD of Sri. R. L. Jalapa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, and Karnataka

The study recruited patients on outpatient basis from December 2011 to April 2012.

The study was started after obtaining ethical clearance from institutional ethical committee.

Inclusion Criteria:-

1. Patients of either gender over 12 years of age
2. Patients with a mycological diagnosis of tinea corporis/tinea cruris

   Confirmed by microscopic KOH wet mount

Exclusion Criteria:-

1. Pregnant and lactating females
2. All other clinical types of tinea infections
3. Patients who are immunocompromised (due to diseases Ex: HIV or medication).
4. Patients with a history of intolerance or hypersensitivity to imidazole and allylamine compounds
5. Patients using the following medications:

a. Topical antifungal agent / topical corticosteroids in treatment area (s) within 30 days of base line visit

b. Systemic antifungals within 8 weeks of base line visit (8 months for oral terbinafine)

c. Systemic corticosteroid within 30 days of base line visit

METHOD OF COLLECTION OF DATA:-

60 Patients were recruited for this Prospective study and patients were alternatively assigned to two groups of 30 patients each.

Group A: - Patients was receiving topical terbinafine

Group B: - Patients was receiving topical luliconazole

Clinical history was taken and clinical evaluation done (after examination) by Dermatologist as per the performa attached. Informed consent was taken from each patient after explaining the details of the study, then patients were assigned to either Group A/Group B and were advised to apply either topical 1% luliconazole cream / topical 1% terbinafine cream at bed time once daily for 14 days.

Complete clinical assessment of main symptoms and signs and mycology screening test (KOH mount) were performed at first visit (base line), at end of corresponding treatment visit (its end of 14^{th} day for both groups) and 15^{th} day and later 30^{th} day.

Improvement in clinical symptoms and signs (pruritus, erythema, scaling) were assessed by scoring them using 4-point scale as scoring[113] done by the investigator (0=absent,1=mild, 2=moderate,3=severe).

Procedure for KOH mount [114,115] :-

Scraping

Infected lesions are scraped from the edge of lesion using scalpel blade no :15 (with pre-flamed blunt scalpel),scrapings may be collected in a black paper or directly on to the slide, KOH 10% (2-3 drops) is added to the collected material, covered by a cover slip and gently preheated before examining for fungi.

Microscopic examination

Slides were microscopically examined first under low power (10x), then under high power (40x) objective, for presence of thin filamentous forms (hyphae).

At the end of treatment & 2-week follow up examination, therapeutic response in each patient was categorized as follows: complete cure- normal microscopy findings, no residual signs & symptoms; mycological cure – normal microscopy findings & mild residual erythema &/or desquamation & /or pruritus(total score ≤ 2),but no other signs & symptoms; improvement – significant reduction in signs & symptoms, but residual signs & symptoms (total score more than 2)& /or presence of pathogen ; failure – no significant response to therapy or exacerbation of signs & symptoms.

If a patient achieved a complete cure or a mycological cure with mild residual signs or symptoms, the response to treatment was considered to be "effective". Therapy was defined as "ineffective" if any other response occurred.[81]

Statistical analysis

The data was analysed for age, sex, duaration of lesion, score pattern & KOH mount. Descriptive statistics was analyzed for demographic data. Duration of lesions between the groups was compared using Unpaired't test. Clinical parameters (pruritus, erythema, scaling) was compared by using Kruskal Wallis test (within the group) and Mann Whitney test for comparing between the groups at base line / 15^{th} day / 30^{th} day.

RESULTS:

Of the 60 patients recruited, all were available for 1st follow- up (15th day) & 51 patients available for 2nd follow up (30th day). All 51 patients were negative for KOH mount preparation on 15th & 30th day.

Table: 4 Demographic details

	1% Terbinafine group n=30	1% Luliconazole group n=30
Age (yrs)	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)

The patients were balanced with respect to baseline characteristics. The mean age was similar in both groups. Majority of the patients were aged between 12-40 years. Male patients predominated in both the study groups.

Table: 5 Duration of lesion at the time of presentation:

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

24 patients of terbinafine group - had 3-20 days as duration and 6 patients of terbinafine group had duration ranging between 21-31 days.

Similarly , among 10 patients of luliconazole group - 5 patients had duration between 3-10 days and the remaining 5 patients had duration between 21-31day . Rest of the 20 patients had duration between 11- 20 days.

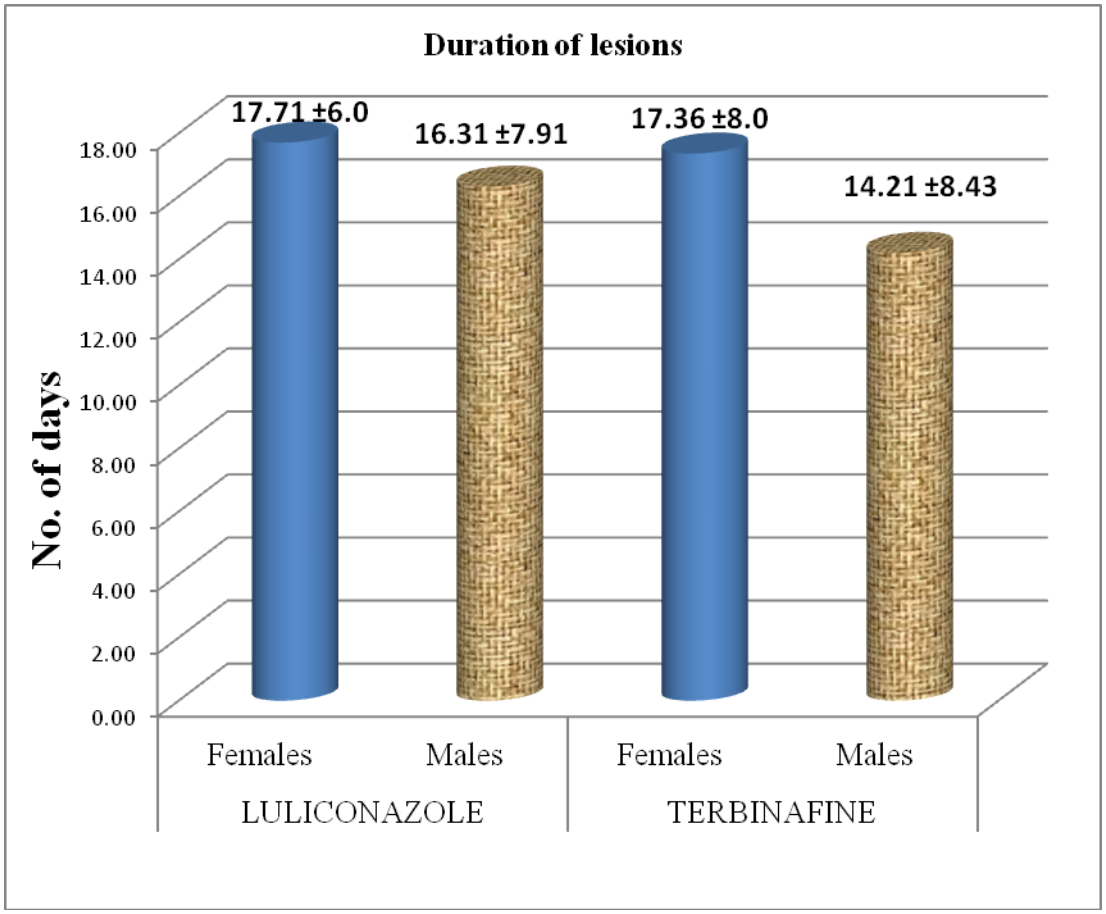


Fig:1 Duration of lesion

Table 5 & figure 1 represents the number of days; the patient was suffering from tinea cruris/tinea corporis before coming to dermatologist.

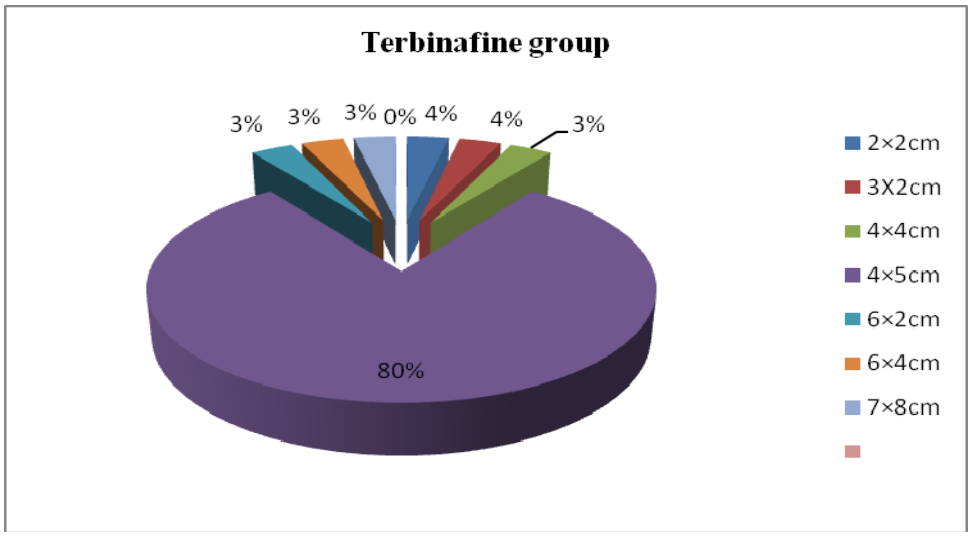


Fig: 2 Terbinafine group (size of lesion)

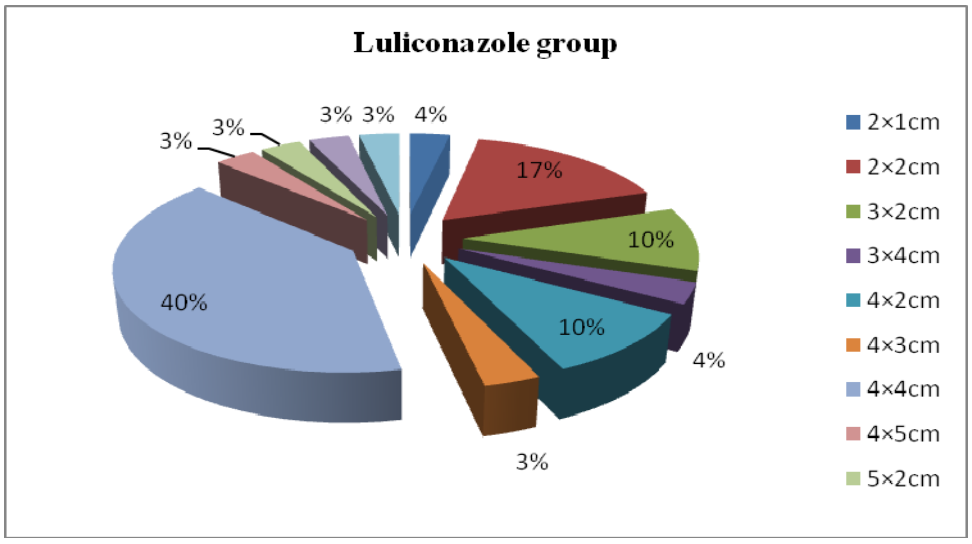


Fig: 3 Luliconazole group (size of lesion)

Fig 2 & 3- Represents the diameter of size of lesions of patients belonging to either of terbinafine / luliconazole group.

Terbinafine group:-

About 80% patients presented with an diameter of 4×5 cm as size of lesion,

remaining 20% patients had an diameter ranging between 2×2cm to 7×8 cm .

Luliconazole group:-

About 40% patients presented with an diameter of 4 ×4 cm as size of lesion,

Remaining 60% patients had a diameter ranging between 2× 1cm to 5× 5cm.

Table: 6 Diagnosis

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

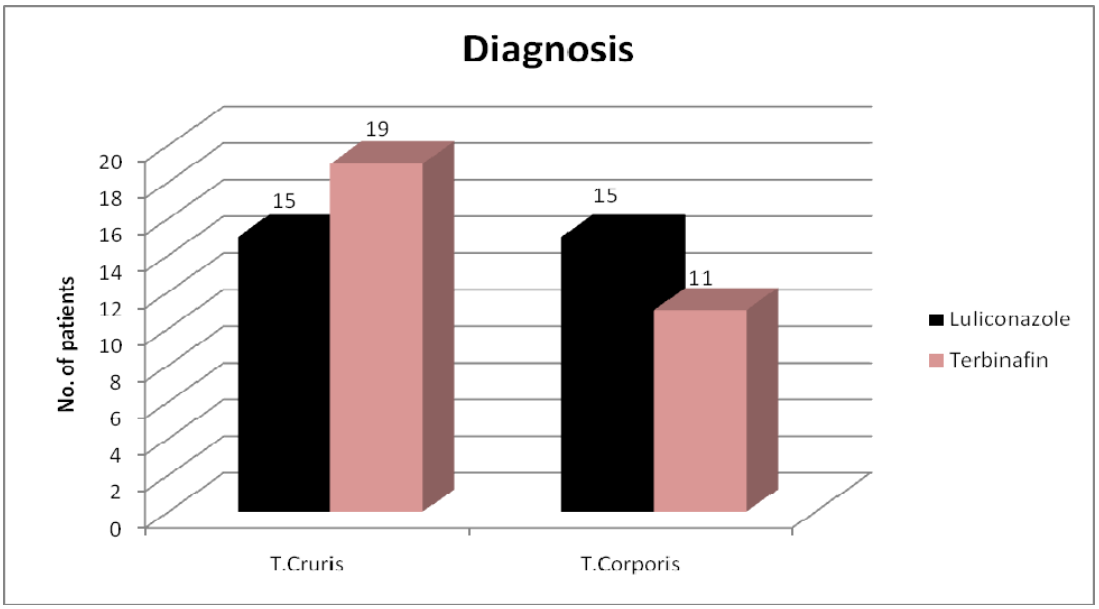


Fig: 4 Diagnosis

Table 6 & figure 4, represents the number of patients being diagnosed as tinea corporis /tinea cruris in the respective groups.

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

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

Table 7:- Responses to treatment in both groups.

Groups	Baseline score=3, KOH mount-positive	15th day, score=0, KOH mount negative	30th day, score=0, KOH mount negative
Terbinafine	30	30	2l
Luliconazole	30	30	25

When the scores were compared within the group there was significant improvement on 15th day compared to baseline in both the groups. The maximum score - 3 & minimum score – 0 KOH mount was negative by 15th day in both the groups, the improvement in symptoms and signs were similar in both the groups by the end of 15th day. (P>0.05) .Type of lesion in both the groups were scaly and erythematous. Complete cure was observed with both the drugs by 15th day. None of the patients had relapse when assessed on day 30. None of the patients reported any serious adverse effects during the entire study period in both the groups. About 4 patients, in terbinafine group showed mild contact dermatitis, which wasn't troublesome issue for their entire treatment & follow up period. No incidence of contact dermatitis was noticed among patients of luliconazole group (P=0.0001).

TERBINAFINE GROUP

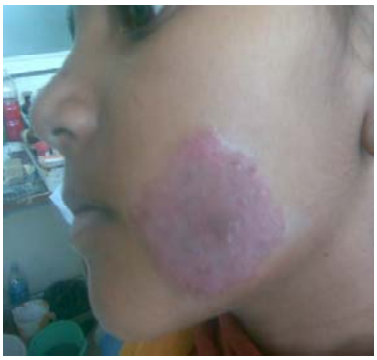


Fig 5a
Base line (Before treatment)

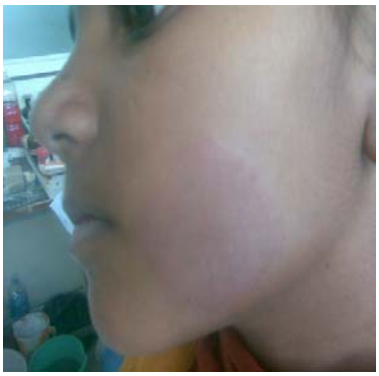


Fig 5b
After 4weeks of treatment completion

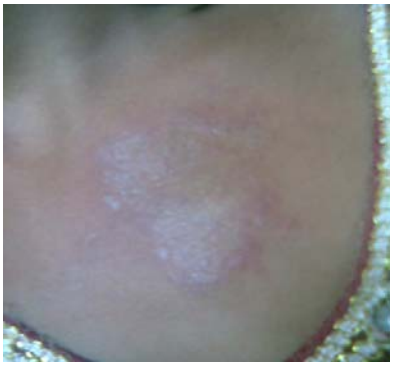


Fig 6a
Base line (Before treatment)

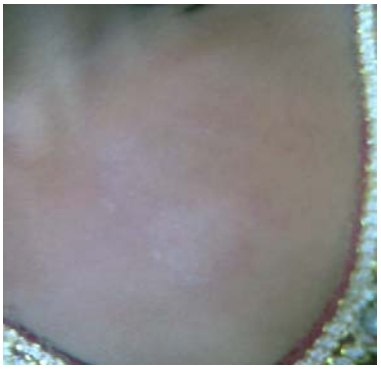


fig 6b
After 4weeks of treatment completion

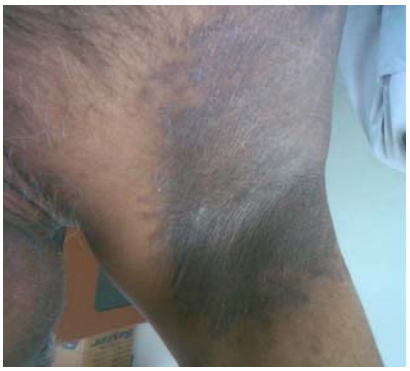


Fig 7a
Base line (Before treatment)

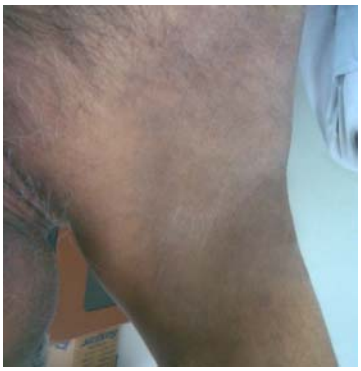


Fig 7b
After 4weeks of treatment completion

LULICONAZOLE GROUP

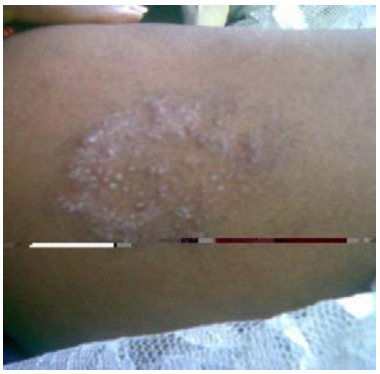


Fig 8a
Base line (Before treatment)

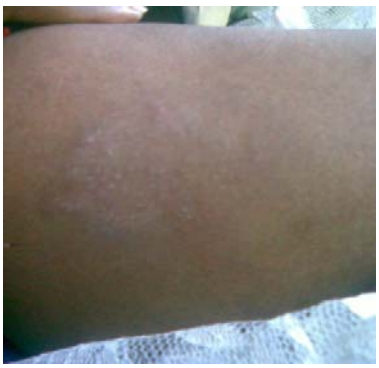


Fig 8b
After 4weeks of treatment completion

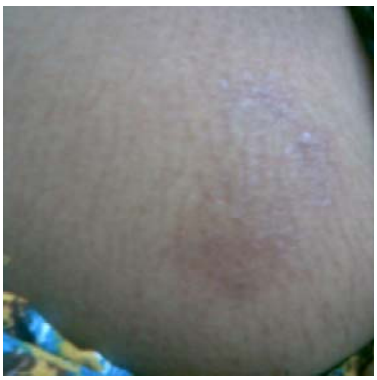


Fig 9a
Base line (Before treatment)

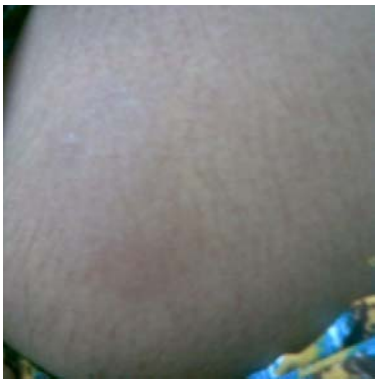


Fig 9b
After 4weeks of treatment completion

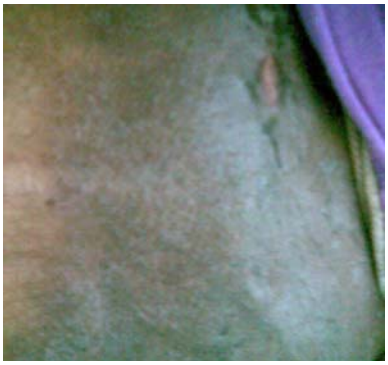


Fig 10a
Baseline (Before treatment)

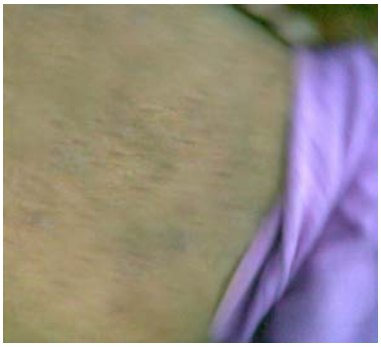


Fig 10b
After 4weeks of treatment completion

Discussion

The treatment for tinea corporis & tinea cruris is extremely varied, current treatment include topical antifungal agents such as clotrimazole, sertaconazole , lanoconazole, miconazole, bifonazole, ketoconazole, terbinafine , which achieve high cure rates but requires almost 2-3 times daily application, for up to 4-6 weeks which can impair patient compliance & lead to treatment failure. An antifungal drug with good efficacy & tolerability with the advantage of providing complete cure in a short duration of treatment may be preferred by the patients and the dermatologists. As there were no clinical studies comparing efficacy of topical terbinafine with topical luliconazole, the present study was undertaken.

In our study, the mean age of patients was 33.80± 9.58 & 33.90± 9.58 years in terbinafine and luliconazole group respectively, which was similar to study done by Budimulja U et al where mean age was 35 yrs.[116] Fifty three patients presented in 2nd, 3rd & 4th decades of life and seven patients in the later years of life as shown in Table 4.

About 80% and 96.6% of patients in terbinafine and luliconazole group respectively were in the age group of 12- 40 years. In the present study, we had only 6 patients of terbinafine group in age group of 41-60 yrs & 1 patient in luliconazole group. The patients in younger age group approach dermatologist in the initial stage of disease itself because of social stigma associated with tinea corporis and cruris and have impact on their day to day life ,as its an contagious infection which spreads, produces itching and disturbs activity and sleep.

Male: female ratio was 1.75 and 1.15 in terbinafine and luliconazole group in our study and was identical to study results of Budimulja et al.[116] The routine outdoor activities of men, make them more aware about their skin disorder, making their life more difficult compared to their female counterpart, as majority of females were homemakers. This could be the reason for increased male predominance in our study & was similar to another study done by Millikan LE et al[86] & Greer DL et al.[81]

The mean duration of lesion in terbinafine group was 15.36 ± 8.28 and luliconazole 16.96 ± 7 days. In this study, there was an early presentation of patients to the dermatologist.

The present study shows that about 80% of patients presented within 3-20 days of disease, both in terbinafine & luliconazole group, in other studies the mean duration of disease at time of presentation was 16–20weeks.[81] none of the patients in this study had a past history of tinea corporis/tinea cruris. Type of lesion in both the groups were scaly & erythematous, which was similar to study done by Budimulja U et al.[116]

In our study, about 36.7 % of patients were of tinea corporis & 63.3 % tinea cruris in terbinafine group and 50% were of tinea corporis & 50 % of tinea cruris in luliconazole group. This shows that percentage of patients presenting with tinea cruris seem to be > more than 50% in both the drug group ,which was also similar to a study findings done by Millikan et al.[86]

About 80% of patients presented with diameter of 4 × 5 cm as size of lesion in terbinafine group & about 40 % of patients with a diameter of 4×4cm in luliconazole group, remaining patients had a diameter ranging between 2 ×2cm to 4×4cm respectively.

We have assessed the response to treatment both by clinical observation(rating them by giving an scoring pattern), as well as with mycological study also i.e. 10% KOH mount, which was done at base line (zero day),end of 15th day & 30th day respectively for both the drug groups. At the end of 15th day, clinical score was '0' and KOH mount was negative in all patients of both the groups. So 2 weeks of treatment with terbinafine and luliconazole has shown to cure tinea corporis and cruris infection. On day 30, 2nd follow-up was done to assess the relapse in the disease condition. 26 and 25 patients came for 2nd follow-up in terbinafine and luliconazole group respectively, and the clinical & mycological assessment score was zero in both the groups, with no statistical difference. Four patients of terbinafine group and 5 patients in luliconazole group were lost to follow-up as they were untraceable or failed to come to hospital after repeated reminders.

Once a day treatment with terbinafine was effective in tinea cruris and corporis for 7 days and the mycological cure was 90% with moderate and severe lesions as related to a study done by Budimulja et al.[116] Hence this study establish the need for 2 week treatment of terbinafine1% for tinea corporis and cruris.

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 4 weeks of follow -up, as compared to 100% at the end of therapy and no cases of relapse at the 4th week follow –up in the present study. Possible reason could be that in the present study only mild forms of tinea were included and duration of illness was 3-

20days, whereas in other studies it was 24 weeks (Millikan et al) [86], 16 weeks (Greer DL et al) [81], & moderate to severe forms of tinea infections were included.

In present study only mild forms of tinea were included, which brought about 100% mycological cure rate in both the drug groups.

Hence 2 week treatment with 1% luliconazole cream is effective in treating mild tinea corporis and cruris infection and its efficacy is comparable to 1% terbinafine.

Maheshwari N et al compared efficacy & safety of luliconazole 1% with miconazole 2% cream in tinea cruris, pedis and corporis patients and showed that the clinical resolution of signs & symptoms was seen in 22.3 and 30.6 days respectively. The time to KOH conversion was 12 days versus 15.6 days & complete cure was 62.9% versus 57.1% in luliconazole & miconazole group respectively. In the present study, clinical improvement and KOH conversion was 100% at the end of 2 weeks of therapy with no relapse at 4th week in luliconazole group.[110]

About 4 patients in terbinafine group showed mild contact dermatitis, which resolved by the end of study period and did not require treatment, which was similar to study done by Greer DL et al.[81] But there were no contact dermatitis among luliconazole group which was statistically significant(P=0.0001). There were no other serious adverse effects in both treatment arms.

CONCLUSION

1.The mean duration of illness in were 15.36 ± 8.28 days & 16.96 ± 7 days in terbinafine & luliconazole group respectively which was less than other study groups.

2. Only mild forms of tinea infections were included when compared to other studies where moderate to severe (pustules, incrustations, vesiculation) were included. Hence the onset of illness, treatment duration and severity of illness were in favor in our study for 2 weeks.

3.Two weeks treatment with terbinafine 1 % cream & luliconazole 1% cream achieved 100% conversion rate (positive KOH mount microscopy to normal microscopy), with 13% & 16% of patients in terbinafine & luliconazole group respectively were lost to follow- up at the end of their 2nd follow-up visit.

4. In both the treatment arms, clinical & mycological cure was comparable.

5. Hence, two weeks once a day application of terbinafine & luliconazole were equally effective for treatment of tinea corporis/cruris infection.

SUMMARY

Tinea infections of skin respond well to topical antifungal therapy, but the need to apply cream 2 – 3 times daily for up to 4 weeks can impair compliance & lead to treatment failure. An agent offering good efficacy & tolerability with a short duration of treatment would provide significant benefits but due to lack of clinical studies, the present study was conducted.

A prospective study was conducted on sixty patients, to be clinically & mycologically diagnosed as tinea corporis/tinea cruris by the dermatologist. Patients were alternatively assigned to either 1% terbinafine or luliconazole group & advised to 1% cream topically, once daily for 14 days. We observed the therapeutic response in terms of mycological cure & clinical scores in both the drug groups.

All 60 patients were available for 1st follow-up (15th day) & 51 patients for 2nd follow-up (30th day).The male to female ratio was 1.75:1.15 in both the drug groups, mean age of the patients was 33.80± 9.58 & 33.90±9.58 years in terbinafine & luliconazole group respectively. About 24 & 25 patients in terbinafine & luliconazole group presented to the dermatologist within 3-20 days of illness.

Response to treatment was assessed, which represents either complete cure/improvement /failure. Clinical symptoms & signs were assessed using 4-point (pruritus, erythema, scaling) scale & 10%KOH mount at base line, end of treatment visit (14th day) & later 30th day. Clinical parameters were compared using Kruskal Wallis test & Mann Whitney test for comparing between groups at baseline/15th day/30th day. When the scores were compared within the group, there was significant improvement on 15th day compared to baseline in both the drug groups. Complete cure was observed with both the drugs by 15th day, mild contact dermatitis was the

adverse effect seen in four patient of terbinafine group which was statistically significant with P=0.0001,which didn't need any discontinuation of therapy, but gradually resolved after completion of treatment period. About 13% & 16% of patients in terbinafine & luliconazole group respectively were lost to follow- up at the end of their 2nd follow-up visit. None of the patients had relapse, when assessed on day 30.

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PROFORMA

1. NAME :
2. AGE :
3. SEX :
4. ADDRESS & CONTACT NO:
5. OCCUPATION :
6. HOSPITAL NUMBER :
7. DATE :
8. PRESENT HISTORY :

a Duration of lesions
b Any medication taken for these lesions
If yes – what medication received?

9. PAST HISTORY :

a Any chronic illness, drug hypersensitivity.
b Any previous history of tinea corporis/tinea cruris
.

10. PERSONAL HISTORY :
11. LOCAL EXAMINATION :

a Area of involvement - Cruris
- Corporis
b Type of lesions - Scaly
- Vesicular
- Erythematous
c Size of lesions.

12. TREATMENT GIVEN : Group A - topical Terbinafine
Group B - topical Luliconazole

13. RESPONSE TO TREATMENT: GROUP A / GROUP B

FOLLOW UP	**O Day(baseline)**		**15th Day**		**30th Day**	
CLINICAL PARAMETERS	**SCORE PATTERN**	**KOH Mount**	**SCORE PATTERN**	**KOH Mount**	**SCORE PATTERN**	**KOH Mount**
Pruritis						
Erythema						
Scaling						
TOTAL						
REMARKS OF CO-GUIDE						

14. OUTCOME: Clinical Efficacy

KEY TO MASTER CHART

SL No.	Serial number
DOL	Duration of lesions
TOL	Type of lesion
SOL	Size of lesion
KOH	Potassium hydroxide mount
A/E	Adverse effects

SL No	SEX	AGE	DOL(days)	DIAGNOSIS	TOL	SOL	SCORE	0 -DAY	15thDAY	30thDAY	KOH	O - DAY	15thDAY	30thDAY	A/E
1	M	30	3	T.Cruris	Scaly,Erythematous			3	0	0		Positive	Negative	Negative	
2	M	45	10	T.Cruris	Scaly,Erythematous	2×2cm		3	0	0		Positive	Negative	Negative	
3	F	25	7	T.Corporis	Scaly,Erythematous	6×4cm		3	0	0		Positive	Negative	Negative	mild dermatitis
4	F	24	7	T.Corporis	Scaly,Erythematous	6×2cm		3	0	0		Positive	Negative	Negative	
5	M	48	15	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	
6	M	37	15	T.Cruris	Scaly,Erythematous	7×8cmB/L		3	0			Positive	Negative		
7	M	19	15	T.Cruris	Scaly,Erythematous	4×5cmB/L		3	0	0		Positive	Negative	Negative	
8	F	36	20	T.Corporis	Scaly,Erythematous	4×2cm		3	0	0		Positive	Negative	Negative	
9	F	37	15	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	
10	M	40	10	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	mild dermatitis
11	M	36	7	T.Corporis	Scaly,Erythematous	2×1cm		3	0	0		Positive	Negative	Negative	
12	M	40	10	T.Corporis	Scaly,Erythematous	5×2cm		3	0			Positive	Negative		
13	F	23	30	T.Corporis	Scaly,Erythematous	2×2cm		3	0	0		Positive	Negative	Negative	
14	M	34	15	T.Cruris	Scaly,Erythematous	3×4cmB/L		3	0			Positive	Negative		
15	M	26	30	T.Cruris	Scaly,Erythematous	3×3cmB/L		3	0	0		Positive	Negative	Negative	
16	F	21	30	T.Corporis	Scaly,Erythematous	10×5cm		3	0	0		Positive	Negative	Negative	mild dermatitis
17	F	42	15	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	
18	M	40	30	T.Cruris	Scaly,Erythematous	6×6cmB/L		3	0	0		Positive	Negative	Negative	
19	M	32	7	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	
20	F	20	22	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	
21	M	46	10	T.Cruris	Scaly,Erythematous	6×6cmB/L		3	0	0		Positive	Negative	Negative	
22	M	59	30	T.Cruris	Scaly,Erythematous	4×2cmB/L		3	0	0		Positive	Negative	Negative	mild dermatitis
23	F	29	15	T.Cruris	Scaly,Erythematous	2×2cmB/L		3	0	0		Positive	Negative	Negative	
24	M	18	20	T.Corporis	Scaly,Erythematous	4×1cmB/L		3	0	0		Positive	Negative	Negative	
25	M	28	4	T.Cruris	Scaly,Erythematous	2×3cmB/L		3	0	0		Positive	Negative	Negative	
26	F	43	10	T.Cruris	Scaly,Erythematous	4×2cmB/L		3	0	0		Positive	Negative	Negative	
27	M	36	20	T.Corporis	Scaly,Erythematous	4×4cm		3	0			Positive	Negative		
28	M	34	7	T.Cruris	Scaly,Erythematous	5×5cmB/L		3	0	0		Positive	Negative	Negative	
29	M	32	12	T.Cruris	Scaly,Erythematous	2×2cmB/L		3	0	0		Positive	Negative	Negative	
30	F	34	20	T.Cruris	Scaly,Erythematous	2×3cmB/L		3	0	0		Positive	Negative	Negative	
TERBINAFINE GROUP															

SL No	SEX	E	DOL(days)	DIAGNOSIS	TOL	SOL	SCORE	0 - DAY	15thDAY	30thDAY	KOH	0 - DAY	15thDAY	30thDAY	A/E
1	M	22	25	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	nil
2	F	18	4	T.Corporis	Scaly,Erythematous	2×2cm		3	0	0		Positive	Negative	Negative	nil
3	F	24	14	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	nil
4	M	39	15	T.Corporis	Scaly,Erythematous	3×2cm		3	0	0		Positive	Negative	Negative	nil
5	M	34	14	T.Cruris	Scaly,Erythematous	4×2cmB/L		3	0			Positive	Negative		nil
6	F	30	15	T.Corporis	Scaly,Erythematous	4×2cm		3	0			Positive	Negative		nil
7	M	18	5	T.Cruris	Scaly,Erythematous	4×2cmB/L		3	0	0		Positive	Negative	Negative	nil
8	M	40	20	T.Cruris	Scaly,Erythematous	6×6cmB/L		3	0	0		Positive	Negative	Negative	nil
9	F	37	25	T.Corporis	Scaly,Erythematous	4×4cm		3	0			Positive	Negative		nil
10	M	39	10	T.Cruris	Scaly,Erythematous	2×2cmB/L		3	0	0		Positive	Negative	Negative	nil
11	M	27	30	T.Cruris	Scaly,Erythematous	4×3cmB/L		3	0	0		Positive	Negative	Negative	nil
12	M	30	31	T.Cruris	Scaly,Erythematous	5×2cmB/L		3	0			Positive	Negative		nil
13	F	38	15	T.Corporis	Scaly,Erythematous	2×2cm		3	0	0		Positive	Negative	Negative	nil
14	M	39	15	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0			Positive	Negative		nil
15	M	30	20	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	nil
16	M	39	4	T.Corporis	Scaly,Erythematous	2×2cm		3	0	0		Positive	Negative	Negative	nil
17	F	18	20	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	nil
18	F	35	15	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	nil
19	M	18	15	T.Cruris	Scaly,Erythematous	5×5cmB/L		3	0	0		Positive	Negative	Negative	nil
20	F	22	30	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	nil
21	M	40	15	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	nil
22	F	27	20	T.Corporis	Scaly,Erythematous	3×2cm		3	0	0		Positive	Negative	Negative	nil
23	F	38	15	T.Cruris	Scaly,Erythematous	4×5cmB/L		3	0	0		Positive	Negative	Negative	nil
24	F	22	20	T.Corporis	Scaly,Erythematous	3×4cm		3	0	0		Positive	Negative	Negative	nil
25	M	27	7	T.Corporis	Scaly,Erythematous	2×1cm		3	0	0		Positive	Negative	Negative	nil
26	F	44	20	T.Corporis	Scaly,Erythematous	4×4cm		3	0	0		Positive	Negative	Negative	nil
27	M	35	15	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	nil
28	F	34	20	T.Cruris	Scaly,Erythematous	2×2cmB/L		3	0	0		Positive	Negative	Negative	nil
29	F	32	15	T.Cruris	Scaly,Erythematous	3×2cmB/L		3	0	0		Positive	Negative	Negative	nil
30	M	30	20	T.Cruris	Scaly,Erythematous	4×4cmB/L		3	0	0		Positive	Negative	Negative	nil
LULICONAZOLE GROUP															