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Review TDD

Topical Luliconazole for the Management of Fungal Infections: A Review

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Abstract

Luliconazole, an antifungal agent of the imidazole class, possesses a distinctive structure where the imidazole component is fused with the ketene dithioacetate configuration. It exists in its R-enantiomer form, which exhibits greater antifungal efficacy compared to lanoconazole, a compound comprising a racemic blend. Strong action is shown by luliconazole against filamentous fungi, such as dermatophytes. The pharmacokinetic characteristics of dermatophytes, such as Trichophyton rubrum and Microsporum gypseum, help explain why they are useful in treating dermatophytic infections. Similar to terbinafine, luliconazole exhibits potent fungicidal activity against Trichophyton spp. Despite being an azole, luliconazole—which comes in two forms-a 1% topical cream and a 10% solution-has demonstrated notable effectiveness in the treatment of diseases like onychomycosis, tinea pedis, and tinea cruris. Luliconazole is more effective than other antifungals such as clotrimazole, its distinct molecular structure also improves penetration into the nail plate. Luliconazole's effective antifungal pastime in vitro and its pharmacokinetic characteristics inside the pores and skin. Even when carried out for a bit period of time-one week for tinea corporis, tinea cruris and two weeks for tinea pedis-luliconazole 1% cream once daily is effective. Japan permitted the usage of 1% luliconazole cream in 2005 to treat tinea infections. The US Food and Drug Administration has simply authorized it for the remedy of tinea corporis, tinea cruris and tinea pedis. Topical luliconazole has a very good protection profile. This evaluation article aims to synthesize modern-day know-how on luliconazole, specializing in its chemical properties, mechanism of action, medical efficacy and application in treating fungal infections.

Keywords: Luliconazole, fungal infections, dermatophytes, antifungal agent, pharmacokinetics

INTRODUCTION

Luliconazole, known by trade name such as Luzu, among others, is an imidazole antifungal drug primarily used as a 1% topical cream. It is indicated for the management of athlete's foot (tinea pedis), ringworm (tinea cruris) and ringworm (tinea corporis) as a result of dermatophytes which include *Trichophyton rubrum, Microsporum gypseum and Epidermophyton floccosum*. Luliconazole, a broad-spectrum antifungal medication, was created in the United States for treating skin and nail infections caused by dermatophytes. It is mainly powerful in opposition to filamentous fungi, including dermatophytes. A contamination of the skin, hair, or nails resulting from dermatophytes, which belong to three genera: *Trichophyton spp.*, *Microsporum spp.*, and Epidermophyton, is known as dermatophytosis. Using a systemic or topical antifungal medication is one of the treatment methods for fungal infections. A vital aspect of the fungal cell membrane is ergosterol. All currently available antifungal agents inhibit the biosynthesis of ergosterol, a vital

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component of the fungal cell wall, thereby preventing fungal growth and reproduction. It has been demonstrated that the imidazole antifungal drug luliconazole has strong action against a wide range of fungi, particularly dermatophytes. According to administration, luliconazole is applied topically to the skin as a 1% cream. It should not be administered orally or intravaginally, nor should it be administered to the eyes. In adults, a typical dose for dermatophytosis (e.g., tinea corporis or tinea cruris) includes applying 1% cream once daily for a week, and for tinea pedis (interdigital) once daily for 2 weeks. The cream should cover the affected area and about 1 inch of surrounding healthy skin. There are no specific dosage recommendations for specific groups and luliconazole is generally well tolerated, with application reactions such as pruritus and pain being the most common side effects. Hence, the present study was conducted to assess the topical luliconazole in management of tinea corporis, tinea cruris and tinea pedis infections [1, 2].

DERMATOPHYTOSIS [3]

Dermatophytes are the maximum commonplace causes of superficial fungal infections worldwide and are huge in developing nations, mainly in tropical and subtropical nations, such as India, wherein the ambient temperature and relative humidity are high. Other factors, which include improved urbanization, consisting of the usage of occlusive footwear and tight garb, have been associated with a higher frequency. Studies on the epidemiology of dermatophytic infection from various parts of India over the past few years have revealed a rising trend in the prevalence of cutaneous dermatophytosis along with changes to the infection spectrum and the isolation of some unusual species.

PATHOGENESIS OF DERMATOPHYTOSIS [3]

Genetics

Not all people are equally susceptible to yeast infection, even if they have similar risk factors. There are signs of a familial or genetic predisposition, which may result from certain defects in innate and adaptive immunity. The pathogenesis of dermatophyte infection entails a complex interplay between the host, the pathogen, and the environment. Predisposing factors for such contamination are underlying sicknesses inclusive of diabetes mellitus, lymphomas, immune deficiency or cushing's syndrome, which can cause severe, widespread, or resistant dermatophytosis. Certain areas of the body are more susceptible to dermatophyte infections, such as the interstices (clefts and groin), where excessive sweating, soaking and alkaline pH encourage fungal growth.

Immunology

The immune system's reaction to dermatophyte infection ranges from humoral and cell-mediated immune responses to non-specific host mechanisms. The prevailing consensus now is that dermatophytosis is within the jurisdiction of the immune system acting through cells.

Mechanism of Luliconazole [4]

Luliconazole is an imidazole antifungal agent primarily used to treat dermatophyte infections. The molecular mechanism of the antidermatophyte activity of luliconazole mainly involves the inhibition of sterol-14α-demethylase, a critical enzyme in the ergosterol biosynthesis pathway in fungal cells. Ergosterol is an essential thing of fungal mobile membranes and its depletion results in accelerated membrane permeability and in the end cellular dying.

ANTIFUNGAL ACTIVITY [5, 6]

Luliconazole, an imidazole antifungal agent, has shown significant activity against dermatophytes, a unique family of keratinophilic molds that cause skin infections. Dermatophytes, together with species of the genera Trichophyton, Microsporum, and Epidermophyton, are not unusual reasons of pores and skin, hair, and nail infections. In particular, species such as *Trichophyton rubrum* and *T. interdigitale* are often isolated from clinical samples, together with other species such as *Epidermophyton floccosum, Trichophyton tonsurans* and *Microsporum canis* (Table 1).

Table 1. Classification of antifungal drugs based on their structure [3].

Antifungal class	Examples
Antibiotics	
Polyenes	Amphotericin B, nystatin, natamycin
Heterocyclic benzofuran	Griseofulvin
Antimetabolite	Flucytosine
Azoles	
Imidazoles	Topical - clotrimazole, econazole, miconazole, bifonazole, fenticonazole, oxiconazole, tioconazole, sertaconazole, berconazole, luliconazole, eberconazole
	Systemic-ketoconazole
Triazoles	Itraconazole, fluconazole (also topical), voriconazole, posaconazole, isavuconazole, posoconazole, ravuconazole, pramiconazole, albaconazol
Allylamines	Terbinafine, butenafine, naftifine
Echinocandins	Caspofungin, anidulafungin, micafungin, aminocandin
Sordarin derivatives	GR135402, GM237354
Cell wall antagonist	Capsofungin, micafungin
Other agents	Tolnaftate, ciclopirox, amorolfine, undecylenic acid, buclosamide, Whitfield's ointment, benzoyl peroxide, zinc pyrithione, selenium sulfide, azelaic acid etc., nikkomycins, icofungipen
Newer and potential therapies	Demcidin, macrocarpal C

AZOLE ANTIFUNGALS [7]

The development of the imidazole organization of antifungal pills become a turning factor in the treatment of superficial and deep mycoses because of their excessive efficacy and occasional toxicity and immune modulating impact. Triazoles, which have three nitrogen atoms in the azole ring, are the other kind of azole. Imidazoles have nitrogen atoms inside the azole ring. They are fungi static except in excessive concentrations, even though they can also be fungicidal. Triazoles have a much better protection profile than imidazoles on account that they have got a more potent affinity for fungus than mammalian P450 enzymes. Imidazoles are only useful in treating superficial mycoses. Currently available topical imidazoles consist of clotrimazole, econazole, ketoconazole, miconazole, noxiconazole, isoconazole, bifonazole, sertaconazole, tioconazole, butoconazole, eberconazole, and luliconazole.

CHEMISTRY AND PHARMACOKINETICS [8]

Luliconazole, also called NND-502, is an imidazole antifungal agent first synthesized via Nihon Nohyaku Co. Ltd. (Osaka, Japan). It has a completely unique structure due to the fact the imidazole moiety is included into the Ketenedithioacetate structure. It's a lanoconazole-like compound featuring a 2,4 Dichlorophenyl group within its ketentioacetal structure. The chemical shape of luliconazole Or (−)-(E)-[4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-1-imidazolylacetonitrile is proven in Figure 1. Just like lanoconazole, the S-enantiomer is inactive, meaning that luliconazole, which is the inactive R-enantiomer, exhibits a stronger antifungal effect compared to lanoconazole. It has been pronounced to have powerful *in vitro* antifungal hobby against *Trichophyton spp., C. Albicans* and *Aspergillus fumigatus*. Luliconazole 1% ointment was authorised in Japan in 2005 for the treatment of skin infections and was authorized by America Food and Drug Administration in November 2013 for treating athlete's foot, jock itch, and ringworm caused by *T. rubrum* and *E. floccosum* in individuals aged 18 and older. It is prescribed to be used once in afternoon for one week for tinea corporis/cruris and for two weeks for tinea pedis. In June 2009, 1% cream changed into permitted for advertising and marketing in India.

Medical Management with Antifungals [3]

Indication of systemic antifungals in dermatophytosis.

- Tinea capitis affecting the scalp hairs (ringworm).
- Onychomycosis affecting the nail plate, nail bed, or both.
- Tinea that affects multiple body regions at once, such as tinea corporis, tinea pedis, and tinea cruris.
- Tinea corporis, in which there are many lesions.
- Tinea pedis can affect the sole, heel or dorsum of the foot.

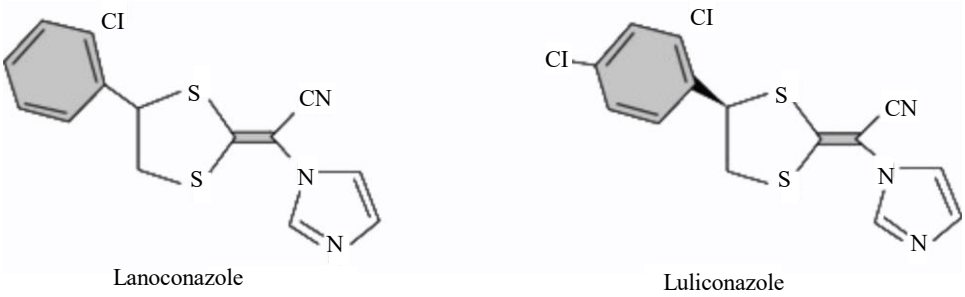

Figure 1. Chemical Structure of lanoconazole and luliconazole [8].

Topical Antifungal Management for Tinea pedis, Tinea corporis and Tinea pedis [9, 10]

A variety of topical antifungal medications are available for the treatment of topical tinea corporis, tinea cruris, tinea faciei and tinea pedis. It can also be used as an adjunct to oral antifungal medications for more extensive infections. Very few researches have examined oral antifungals, while the majority of studies on the treatment of tinea corporis and cruris have examined the efficacy of topical antifungals. As shown in Table 2, topical antifungals are typically used once or twice daily for a period of two to four weeks. In the majority of instances, clinical resolution is the goal of treatment. Topical antifungals with powerful anti-inflammatory action which includes sertaconazole or luliconazole may be a better choice than an antifungal-steroid combination. A topical antifungal cream is typically used to treat tinea pedis for four weeks; however, interdigital tinea pedis may only need one week of treatment. A meta-analysis shows strong evidence that different types of topical antifungal medications, such as azoles, allylamines, butenafine, ciclopirox, tolnaftate, and amorolfine, are more effective against tinea pedis than placebo.

Table 2. Topical antifungals used in the treatmentof tinea pedis, tinea corporis and tinea cruris [3].

Azole	Preparations	Site	Frequency of application	Duration of use
Imidazoles (%)				
Clotrimazole (1)	Cream, lotion	T. corporis/cruris/pedis	BD	4–6 weeks
Econazole (1)	Cream	T. corporis/cruris/pedis	OD-BD	4–6 weeks
Miconazole (1)	Cream, lotion	T. corporis/cruris/pedis	BD	4–6 weeks
Oxiconazole (2)	Cream, lotion	T. corporis/cruris/pedis	OD-BD	4 weeks
Sertaconazole (2)	Cream	T. corporis/cruris/pedis	BD	4 weeks
Luliconazole (1)	Cream, lotion	T. corporis/cruris/pedis	OD	2 weeks
Eberconazole (1)	Cream	T. corporis/cruris/pedis	OD	2–4 weeks
Triazoles (%)				
Efinaconazole (10)	Solution	T. pedis	OD	Up to 52 weeks in co-existing tinea unguium
Allylamines				
Terbinafine	Cream, powder	T. corporis	BD	2 weeks
		T. cruris	BD	2 weeks
		T. pedis	BD	4 weeks
		T. manuum	BD	4 weeks
Naftifine 1%	Cream	T. corporis/cruris/pedis	OD-BD	Use 2 weeks beyond resolution of symptoms
Butenafine 1%	Cream	T. corporis/cruris/pedis	OD-BD	2–4 weeks
Others				
Amolorfine 0.25%	Cream	T. corporis	BD	4 weeks
Amphotericin B (1 mg) 0.1%	Lipid based gel	T. corporis	BD	2 weeks

T. corporis: Tinea corporis, T. pedis: Tinea pedis, T. manum: Tinea manum, T. cruris: Tinea cruris

Newer Topical Antifungals [11, 12]

Luliconazole, an azole antifungal, has fungicidal activity in opposition to Trichophyton species just like or more potent than terbinafine. Available as a 1% cream, it's far powerful once daily for dermatophyte contamination for 1-2 weeks. US FDA approved for the treatment of interdigital tinea pedis, tinea cruris and tinea corporis with a positive protection profile. The composition of Econazole nitrate foam has additionally been proven to be powerful within the remedy of tinea pedis. However, those newer drugs are extra luxurious, which in turn can reason troubles with adherence to treatment in aid-terrible environments and promote predisposition. Finally, it promises to apply a unique delivery gadget wherein the figure drug is related to vendors together with micelles, or using nanostructured lipid-primarily based carriers, microemulsions and vesicular structures consisting of liposomes, niosomes, transfersomes, ethosomes or penetration-selling ones.

CONCLUSION

Emerging as a strong and adaptable antifungal drug, luliconazole is especially useful against dermatophytes, the microorganisms that cause a variety of infections of the skin, hair, and nails. It is a useful treatment choice for dermatophytic infections because of its broad-spectrum activity against dermatophytes, yeasts, and other fungi. The imidazole and dichlorobenzene rings that make up luliconazole's chemical structure help to explain its antifungal effects. By blocking sterol 14α-demethylase in the ergosterol production pathway, it causes fungal cell death. This is how it works. Because of this special activity as well as its excellent penetration of the epidermal layers and nail plate, luliconazole represents a major breakthrough in antifungal therapy. All things considered, luliconazole sticks out as an essential addition to the toolbox of antifungal treatments, providing a wealth of advantages in terms of effectiveness, safety, and affordability. Its creation and application represent a major advancement in the treatment of dermatophyte-caused fungal diseases. Luliconazole is a powerful and focused choice for treating dermatophytosis, and it marks a substantial development in antifungal therapy. Its promise as a first-line treatment for a variety of infections associated to dermatophytes is highlighted by its broad-spectrum efficacy and advantageous pharmacokinetic characteristics. Future studies on luliconazole should concentrate on its long-term effectiveness, resistance trends, and possible systemic uses. It may be concluded, given the constraints of this study, that topical luliconazole is very efficient in treating infections of tinea corporis, tinea cruris and tinea pedis.

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