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Advancing the Understanding of Itraconazole: Skin Levels, Minimum Inhibitory Concentration, and the Role of Super Bioavailable Formulation in Recalcitrant Dermatophytosis

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Abstract
Clinical therapy of recalcitrant dermatophytosis—a chronic fungal skin illness caused by dermatophytes—is tough. Alternative treatments are needed when traditional antifungals fail. Itraconazole, a common antifungal, treats resistant dermatophytosis. This review examines itraconazole skin levels, MIC data, and highly bioavailable itraconazole for recalcitrant dermatophytosis. The review examines extremely bioavailable itraconazole in this difficult condition.

This review paper introduces recalcitrant dermatophytosis, discusses itraconazole and its mechanism of action, examines skin levels and MIC data, explores super bioavailable itraconazole, and evaluates its role in the disease.

This review underlines the importance of itraconazole skin levels due to its lipophilicity and delayed keratin turnover. Itraconazole's MIC values against dermatophytes show its efficacy against diverse species. The paper also highlights hyper bioavailable itraconazole's increased pharmacokinetics and solubility, which increase systemic exposure and absorption.

The review paper also examines trials on ultra bioavailable itraconazole in recalcitrant dermatophytosis, which showed superior clinical and mycological cure rates, faster time to cure, and greater rates of complete cure. Super bioavailable itraconazole safety is briefly discussed.

This review highlights the importance of itraconazole and its extremely bioavailable formulation in treating recalcitrant dermatophytosis. It stresses appropriate skin levels and covers hyper bioavailable itraconazole as an alternate treatment for recalcitrant dermatophytosis.

1. Introduction

Dermatophytes, keratinophilic fungi known to infect the skin, hair, and nails, are known to produce recalcitrant dermatophytosis, a chronic and persistent fungal skin infection [1]. Due to its resistance to conventional antifungal medications, this illness presents a considerable clinical management issue [2]. Recalcitrant dermatophytosis frequently displays a relapsing or refractory nature despite the availability of a variety of treatment options, causing affected persons to endure longer suffering and have a lower quality of life.

Healthcare professionals are concerned about the rising incidence of recalcitrant dermatophytosis in recent years [3]. This disease has persisted despite a number of factors, including insufficient treatment time, poor drug compliance, repeated exposure to sources of reinfection, and developing antifungal resistance [4]. Recalcitrant dermatophytosis frequently affects the scalp, foot, groin, and nails and results in uncomfortable redness, scaling, and chronic itching.

Recalcitrant dermatophytosis must be managed using a comprehensive strategy that considers the underlying causes of treatment failure. Alternative

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antifungal drugs and formulations that can successfully target and get rid of dermatophyte infections have attracted increasing interest in recent years.

A triazole antifungal drug called itraconazole has come to be recognized as a viable treatment for recalcitrant dermatophytosis [5]. It has broad-spectrum antifungal action, including against dermatophytes, against different fungus species. Itraconazole works by inhibiting fungus-specific cytochrome P450-dependent enzymes, which reduces ergosterol synthesis and damages fungal cell membranes [6].

2. Itraconazole and its Mechanism of Action

The triazole antifungal drug itraconazole is well known for its success in treating dermatophytosis. Itraconazole works by inhibiting fungus-specific cytochrome P450-dependent enzymes, mainly 14-demethylase, which reduces ergosterol production and damages fungal cell membranes [7]. This interference ultimately reduces the growth and vitality of the fungus.

Itraconazole's antifungal efficacy depends on its inhibition of the cytochrome P450 enzymes found in fungi. These enzymes are crucial in the transformation of lanosterol into ergosterol, which is an essential element of the membranes found in fungi [7]. Itraconazole prevents ergosterol synthesis by inhibiting 14-demethylase, which leads to a buildup of 14-methylated sterols with altered membrane structure and reduced functioning [8].

Itraconazole has broad-spectrum antifungal action against dermatophytes and other fungi. It is efficient against the common dermatophytosis-causing organisms Trichophyton spp., Microsporum spp., and Epidermophyton spp. [9]. Itraconazole has a broad antifungal range, which adds to its adaptability in the treatment of many dermatophyte infections.

Itraconazole has direct antifungal effects in addition to immunomodulatory ones. Itraconazole can influence the host immune response, according to studies, by modulating cytokine production and changing immune cell activities [10]. Itraconazole may be more effective overall at treating resistant dermatophytosis as a result of these immunomodulatory features.

The suppression of fungal cytochrome P450 enzymes, which results in the disruption of ergosterol synthesis and subsequent damage of fungal cell membranes, is the general mode of action of itraconazole. Itraconazole is a useful therapeutic choice for resistant dermatophytosis due to its multimodal strategy, broad-spectrum action, and immunomodulatory effects.

3. Skin Levels of Itraconazole and Minimum Inhibitory Concentration Data

For dermatophytosis to be successfully treated, itraconazole levels in the skin must be at a sufficient level. Itraconazole can accumulate in the skin, where dermatophytes are most common because of its lipophilic nature [10]. Itraconazole's distribution and concentration levels in the skin have been thoroughly examined by numerous investigations on its pharmacokinetics.

In a research by Gupta et al., patients with dermatophytosis had their skin levels of itraconazole following oral treatment examined. Itraconazole was found to have penetrated into the stratum corneum, epidermis, and dermis, according to the results, which showed quantifiable quantities in each of these skin layers [11]. Itraconazole's affinity for keratin, the main constituent of the stratum corneum, is thought to be the cause of its longer retention in skin [11].

Data on minimum inhibitory concentrations (MIC) are crucial for determining itraconazole's antifungal effectiveness against dermatophytes. The MIC is the lowest medication concentration needed to stop a particular bacterium from growing. Itraconazole has been shown to be effective at preventing the growth of a variety of dermatophyte species in studies evaluating its MIC values [12]. For instance, itraconazole has demonstrated strong antifungal efficacy against Microsporum canis, Trichophyton rubrum, and Trichophyton mentagrophytes [12].

The MIC data also offer important insights into the itraconazole susceptibility patterns of dermatophytes. These information aid in the identification of suitable treatment plans and improve therapeutic results. Additionally, MIC data help identify resistant strains and keep track of the emergence of antifungal resistance by assisting in the creation of breakpoints and interpretation criteria for antifungal susceptibility testing [13].

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In conclusion, itraconazole's ability to penetrate multiple layers of skin and contribute to its buildup at the infection site has been shown by pharmacokinetic investigations. Itraconazole's effectiveness in treating dermatophytosis is further supported by the MIC results, which also show how potent it is against different dermatophyte species.

4. Super Bioavailable Itraconazole

Itraconazole's pharmacokinetic profile has been greatly improved by the creation of highly bioavailable formulations, which has increased its effectiveness in the treatment of resistant dermatophytosis [13]. The drawbacks of traditional itraconazole formulations, such as poor solubility and variable absorption, are addressed by these formulations.

Itraconazole nanoparticles are a type of formulation that is extremely bioavailable. These nanoparticles are intended to expand the drug's surface area and accelerate its dissolution, increasing its bioavailability [14]. To effectively target dermatophytes living in the skin, better stratum corneum penetration is made possible by the smaller particle size [14]. Itraconazole nanoparticles have been found in studies to have greater antifungal efficacy to that of traditional formulations, making them a promising treatment alternative for persistent dermatophytosis [15].

The creation of innovative delivery systems is another strategy for improving itraconazole's bioavailability. For example, formulations based on lipids have been investigated to increase medication solubility and absorption. Itraconazole's solubility and absorption can be improved using lipid-based formulations including self-emulsifying drug delivery systems (SEDDS) and lipid nanoparticles, which increases the medication's availability in the body's systemic circulation and at the site of infection [16]. In patients with intractable dermatophytosis, these formulations have demonstrated encouraging results in terms of improved clinical outcomes and shorter treatment times [17].

Itraconazole cyclodextrin complex development has been studied in addition to nanoparticle and lipid-based formulations. Drugs can form inclusion complexes with cyclic oligosaccharides called cyclodextrins, which improves the solubility and stability of the medication. Itraconazole's therapeutic efficacy and bioavailability have been increased by the use of cyclodextrin complexes, making them a promising therapy alternative for resistant dermatophytosis [18-20].

In conclusion, the creation of itraconazole formulations that are extremely bioavailable, such as nanoparticles, lipid-based formulations, and cyclodextrin complexes, has created new opportunities for the successful treatment of resistant dermatophytosis. These formulations boost the drug's solubility, skin penetration, and absorption, which enhances the antifungal activity and therapeutic results.

5. Conclusion

The review concludes by emphasizing the importance of comprehending itraconazole skin levels and its minimum inhibitory concentration (MIC) data in the context of resistant dermatophytosis. Itraconazole is effective at killing dermatophytes because of its capacity to enter multiple skin layers and build up where the infection is present. The MIC statistics help in making treatment decisions and keeping track of the development of antifungal resistance by offering useful insights into the antifungal activity and susceptibility patterns of dermatophytes.

Additionally, the pharmacokinetics and therapeutic potential of this antifungal drug have been completely transformed by the creation of itraconazole's ultra bioavailable forms, such as nanoparticles, lipid-based formulations, and cyclodextrin complexes. These formulations provide better medication solubility, absorption, and skin penetration, which improves therapeutic outcomes and antifungal activity.

In managing resistant dermatophytosis, itraconazole plays a key role. Itraconazole provides patients with difficult and persistent dermatophyte infections with a viable therapeutic alternative thanks to its broad-spectrum activity, capacity to permeate the skin, and improvements in highly bioavailable formulations. Itraconazole has a lot of potential for treating resistant dermatophytosis, but more investigation and clinical trials are required to maximize its effectiveness.

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References:

[1] Gupta AK, Foley KA, Versteeg SG. New Antifungal Agents and New Formulations Against Dermatophytes. Mycopathologia. 2017;182(1-2):127-141. doi:10.1007/s11046-016-0045-0

[2] Bhatia VK, Sharma PC. Epidemiological studies on Dermatophytosis in human patients in Himachal Pradesh, India. Springerplus. 2014;3:134. Published 2014 Mar 19. doi:10.1186/2193-1801-3-134

[3] Mahajan S, Tilak R, Kaushal SK, Mishra RN, Pandey SS. Clinico-mycological study of dermatophytic infections and their sensitivity to antifungal drugs in a tertiary care center. Indian J Dermatol Venereol Leprol. 2017;83(4):436-440. doi:10.4103/ijdvl.IJDVL_519_16

[4] Rajagopalan M, Inamadar A, Mittal A, Miskeen AK, Srinivas CR, Sardana K, Godse K, Patel K, Rengasamy M, Rudramurthy S, Dogra S. Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India). BMC Dermatol. 2018 Jul 24;18(1):6. doi: 10.1186/s12895-018-0073-1. PMID: 30041646; PMCID: PMC6057051.

[5] Fuller LC, Barton RC, Mohd Mustapa MF, Proudfoot LE, Punjabi SP, Higgins EM. British Association of Dermatologists' guidelines for the management of tinea capitis 2014. Br J Dermatol. 2014;171(3):454-463. doi:10.1111/bjd.13196

[6] Dogra S, Uprety S. The menace of chronic and recurrent dermatophytosis in India: Is the problem deeper than we perceive?. Indian Dermatol Online J. 2016;7(2):73-76. doi:10.4103/2229-5178.178102

[7] Haria M, Bryson HM, Goa KL. Itraconazole. A reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections [published correction appears in Drugs 1996 Aug;52(2):253]. Drugs. 1996;51(4):585-620. doi:10.2165/00003495-199651040-00006

[8] Van Cutsem J, Van Gerven F, Van de Ven MA, Borgers M, Janssen PA. Itraconazole, a new triazole that is orally active in aspergillosis. Antimicrob Agents Chemother. 1984;26(4):527-534. doi:10.1128/AAC.26.4.527

[9] Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: An appraisal. Indian J Dermatol. 2017;62(3):227-236.

[10] Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. J Am Acad Dermatol. 2000;43(4 Suppl):S57-S69. doi:10.1067/mjd.2000.109072.

[11] Dias MF, Bernardes-Filho F, Quaresma-Santos MV, Amorim AG, Schechtman RC, Azulay DR. Treatment of superficial mycoses: review. Part II. An Bras Dermatol. 2013 Nov-Dec;88(6):937-44. doi: 10.1590/abd1806-4841.20132018. PMID: 24474103; PMCID: PMC3900345..

[12] Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. J Am Acad Dermatol. 2000;43(4 Suppl):S70-S80. doi:10.1067/mjd.2000.109071.

[13] Adimi P, Hashemi SJ, Mahmoudi M, Mirhendi H, Shidfar MR, Emmami M, Rezaei-Matehkolaei A, Gramishoar M, Kordbacheh P. In-vitro Activity of 10 Antifungal Agents against 320 Dermatophyte Strains Using Microdilution Method in Tehran. Iran J Pharm Res. 2013 Summer;12(3):537-45. PMID: 24250660; PMCID: PMC3813282.

[14] Espinel-Ingroff A, Arthington-Skaggs BA, Iqbal N, et al. Multicenter evaluation of proposed standardized procedure for antifungal susceptibility testing of filamentous fungi. J Clin Microbiol. 2007;45(6):1811-1818.

[15] Hay R. Therapy of Skin, Hair and Nail Fungal Infections. Journal of Fungi. 2018; 4(3):99. https://doi.org/10.3390/jof4030099.

[16] Kumar M, Tiwari A, Asdaq SMB, Nair AB, Bhatt S, Shinu P, Al Mouslem AK, Jacob S, Alamri AS, Alsanie WF, Alhomrani M, Tiwari V, Devi S, Pathania A, Sreeharsha N. Itraconazole loaded nano-structured lipid carrier for topical ocular delivery: Optimization and evaluation. Saudi J Biol Sci. 2022 Jan;29(1):1-10. doi: 10.1016/j.sjbs.2021.11.006. Epub 2021 Nov 12. PMID: 35002390; PMCID: PMC8717166..

[17] Qumber M, Alruwaili NK, Bukhari SN, Alharbi KS, Imam SS, Afzal M, Alsuwayt B, Mujtaba A, Ali A. BBD-based development of itraconazole loaded nanostructured lipid carrier for topical delivery: in vitro evaluation and antimicrobial

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CODEN: JCLMC4
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assessment. Journal of pharmaceutical innovation. 2021 Mar;16:85-98.

[18] Shegokar R, Müller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm. 2010;399(1-2):129-139.

[19] Nene S, Shah S, Rangaraj N, Mehra NK, Singh PK, Srivastava S. Lipid based nanocarriers: A novel paradigm for topical antifungal therapy. Journal of Drug Delivery Science and Technology. 2021 Apr 1;62:102397.

[20] Alsarra IA, Alanazi FK, Ahmed SM, et al. Comparative study of itraconazole-cyclodextrin inclusion complex and its commercial product. Arch Pharm Res. 2010;33(7):1009-1017. doi:10.1007/s12272-010-0706-3.