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Efficacy of supra bioavailable itraconazole and conventional itraconazole at different dosing regimens in glabrous tinea infection

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Abstract:

Background & Methods: The aim is to study Efficacy of super-bioavailable itraconazole 130 mg and conventional-itraconazole 100 mg twice daily in glabrous tinea infection. Patients with KOH positive were given itraconazole in two different formulation. Patient with KOH negative were declared clinically cure.

Results: We found KOH-negative Patient (After treatment) in Group A as super-bioavailable itraconazole 130 mg with 54% whereas Group B as conventional-itraconazole 100mg with 46%. (p=0.271669)

Conclusion: Super-Bioavailable itraconazole 130 mg has better pharmacokinetic profile than conventional itraconazole 100 mg. This may not reflect in the form of better efficacy and safety than in the treatment of dermatophytosis. Multiple other factors might have a role to play in the lack of adequate clinical response of dermatophytosis to itraconazole. We could not find any better efficacy or safety of SB itraconazole as compared to conventional itraconazole.

Keywords:

Efficacy, bioavailable, itraconazole, glabrous & tinea.

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Introduction

Over the past few years, a steep surge in dermatophytosis or glabrous tinea has been reported by many folds, especially in India, along with an increase in chronic and recurrent presentation and relapse rates of dermatophytosis[1]. Drug additionally, there is an immense discrepancy between the management of dermatophytosis in the current scenario and treatment guidelines given in standard dermatology text books.

In the past few years, India has witnessed a precipitous surge in incidence of dermatophytosis and therefore in the prescription of systemic antifungal drugs. Because of this changing face, the majority of dermatologists in India are relying on multiple experience-based treatment strategies such as higher dose of antifungal and increased duration of treatment[2]. Although itraconazole (ITZ) is the most commonly prescribed systemic antifungal due to its potency, it has poor gastrointestinal tolerability, intra- and inter-patient variations in bioavailability, and must be taken with food for better absorption, all of which limit its use[3]. In one study on serum concentration of ITZ by Wiederhold et al., only 55.4% of patients were found to have serum concentrations above 500 ng/mL, a reference level set in invasive fungal infections. Additionally, it was found that sebum levels of ITZ were ten times as high as the corresponding peak plasma levels; therefore, sebum concentrations of ITZ become more important when used for the management of dermatophytosis[4].

A new formulation, super-bioavailable ITZ (SBITZ) has been recently launched in many countries as

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130 mg capsules and in the United States as 65 mg capsules. This new formulation contains a solid dispersion of ITZ in a pH-dependent polymeric matrix, named hydroxypropyl methylcellulose phthalate, which enhances both dissolution and intestinal absorption and is claimed to swamp the pharmacokinetic challenges associated with conventional ITZ (CITZ). Recently, in India, many strengths of SBITZ were approved by the Central Drug Standard Control Organization (CDSCO, central licensing authority) in dosages of 50, 65, 100 and 130 mg, which has created dilemma at physician level[5-7].

Material and Methods

Present study was conducted at AIMS, Dewas, (M.P) for 01 Year from december 2023 to december 2024. All diagnoses were confirmed by direct microscopy under 10% potassium hydroxide (KOH mount). KOH mounts were made from all active clinical lesions and all fields within each smear were examined at 40 × magnification. No special stains were added for microscopic examination of the skin scrapings. Liver function tests (LFTs) were performed at baseline and at the end of the treatment.

Patients in Group A received oral conventional Itraconazole 100mg BID with food and the patients in Group B received Oral SB Itraconazole 130mg BID irrespective of food intake for 3 weeks and then followed by 6 weeks. Following this treatment period, patients with complete cure were not prescribed any antifungal medication, whereas the remaining patients were allowed to take antifungal medication till they became KOH negative. Scoring of the Dermatology Life Quality Index (DQLI) was performed at the same visit and at the end of treatment.

Inclusion Criteria:

Adult patients (≥ 18 years and ≤ 60 years) of either sex with glabrous tinea requiring systemic antifungal therapy, with no history of intake of any oral antifungal agent in the preceding four weeks or a topical antifungal/steroid in the preceding two weeks, were recruited. Additionally, patients with chronic dermatophytosis with duration of ≥6 months and no use of antifungals for the last 4 weeks were recruited.

Exclusion Criteria:

Patients who were pregnant, lactating, or had any significant medical illnesses, such as metabolic diseases or immunocompromised conditions, that would have affected the clinical outcomes were excluded from the study. Patients taking concomitant medications that interact with itraconazole were also excluded. All female patients of childbearing age were advised to avoid pregnancy during the treatment.

Result

Table No. 1: Baseline Characteristics

S. No.	Parameter	Group A	Group B	P Value
1	Age in Year	35.97±6.52	35.12±9.04	
2	Duration in Month	8.71±6.11	6.65±8.78	
3	Gender	Group A	Group B	.414216
	Male	(22)44%	(18)36%	
	Female	(28)56%	(32)64%	

The mean age of patients in Group A was 35.97±6.52 years and in Group B was 35.12±9.04 years and was comparable between the 2 groups. The mean duration of disease in Group A was 8.71±6.11 months and in Group B was 6.65±8.78 months with no statistically significant difference between the 2 groups.
The chi-square statistic is 0.6667. The p-value is .414216. The result is not significant at $p < .05$.

Table No. 2: Frequency of disease variability in groups

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Journal of Dermatological Case Reports

S. No.	Parameter	Group A	Group B	P Value
1	T. Cruris	(15)31%	(18)36%	.047824
2	T. Corporis	(05)10%	(06)13%	
3	T. Cruris/corporis	(26)53%	(25)50%	
4	T. Cruris/Faciei	(02)03%	(01)01%	
5	T. Cruris/corporis/ Faciei	(02)03%	(00)00%	

The chi-square statistic is 4.676. The p-value is .047824. The result is significant at $p < .05$.
Tinea cruris was the predominant form in either group.

Table No. 3: Response to KOH test from different formulation of Drugs

S. No.	Parameter	Group A	Group B	P Value
1	Baseline	249.70±16.30	247.93±4.99	0.271669
2	Follow-up	233.16±13.24	232.69±6.55	
3	KOH-negative Patient (After treatment)	(27)54%	(23)46%	

We found KOH-negative Patient (After treatment) in Group A 54% whereas Group B 46%. (p=0.271669)

Discussion

The experts opined that different formulations of ITZ may be compared using fungal culture; sensitivity analysis; potassium hydroxide mount; antifungal activity assay; polymerase chain reaction studies; molecular studies; and blood, serum, and sebum concentrations of the drug[8]. The experts also opined that these studies can be performed at an interval of 4, 6, 8, or 12 weeks of treatment based on uniform guidelines or consensus based on clinical experience. As per the expert opinions, although the patient's premedication history is obtained from their feedback, some patients may hide their history of using nonsteroidal anti-inflammatory drugs for pain relief[9]. Patients without premedication history are usually prescribed ITZ-C for 1-1.5 months, but baseline investigations are often not possible as many patients refuse testing due to financial concerns. Treatment is based on patient feedback, which can be unreliable due to hidden medication history. Clinicians often prescribe ITZ-C for 4-6 weeks and then perform liver function tests for new patients. The irregularity of patient follow-up and treatment adherence can also pose challenges for clinicians. However, the treatment regimen varies as per the clinical experience of dermatologists or clinicians[10].

ITZ has complex and highly variable pharmacokinetics, especially after oral administration. It follows nonlinear pharmacokinetics in a comparison of single versus multiple-dose administration. Because of non-linearity in pharmacokinetics, there is a disproportionate increase in ITZ plasma concentration. Heykants et al. and Hardin et al. have concluded that oral absorption and bioavailability of ITZ are a function of dose. Non-linear increase in the AUC and Cmax were reported after oral doses of 50, 100 and 200 mg, pointing out a saturation of the first-pass metabolism process in the liver[11].

Nevertheless, sebum concentrations of all formulations were found to be above the minimum inhibitory concentration (MIC) levels of ITZ. Shaw et al. demonstrated MICs of ITZ against Trichophyton mentagrophytes in the ranges 7.8–1000 ng/mL. This could be due to higher sebum concentration achieved in SB 130 mg OD group in the present study as compared to other strengths of ITZ, which might result in more consistent delivery of the drug at target site, that is, the skin, and led to extensive fungal eradication as seen in efficacy parameters. Second, the duration of treatment was also for 4 weeks in this study, which might have led to a lower number of patients achieving complete

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cure in all groups; however, this difference was not statistically significant[12].

In case of systemic antifungals, the concentration attained at the site of infection is one of the most critical factors governing its efficacy. ITZ, being a lipophilic drug, is excreted in sebum and stratum corneum concentrations are important in dermatophytosis. The concentration of ITZ in sebum is crucial as its distribution in the skin, especially stratum corneum, is extensively dependent on sebum production.

Conclusion

Super Bioavailable itraconazole has better pharmacokinetic profile than conventional itraconazole. This may not reflect in the form of better efficacy and safety than in the treatment of dermatophytosis. Multiple other factors might have a role to play in the lack of adequate clinical response of dermatophytosis to itraconazole. We could not find any better efficacy or safety of SB itraconazole as compared to conventional itraconazole.

The super bioavailable formulation, ITZ-SB (130 mg), has exhibited greater efficacy in managing dermatophytosis, improved bioavailability, and reduced interindividual variability; it is particularly beneficial in patients who have a history of steroid abuse or are on PPIs. This novel formulation surpasses the currently available therapies and could lead to better patient compliance due to smaller pill sizes and flexible dosing, thereby making it a promising candidate for the treatment of dermatophytosis.

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