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COMPARATIVE BIOCHEMICAL SAFETY OF ITRACONAZOLE AND TERBINAFINE IN SUPERFICIAL DERMATOPHYTOSIS: APROSPECTIVE STUDY

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ABSTRACT: Objectives: Systemic antifungal therapy is widely used for dermatophytosis, but concerns regarding biochemical safety and adverse effects remain clinically relevant. This study aimed to compare the biochemical safety profile of oral itraconazole and terbinafine in patients with superficial dermatophytosis. **Methods:** In this prospective comparative clinical study, 180 adult patients with potassium hydroxide-confirmed superficial dermatophytosis were allocated into two groups (n=90 each). Group A received oral itraconazole 100 mg twice daily, and Group B received oral terbinafine 250 mg once daily for six weeks, and both groups received topical clotrimazole. Biochemical parameters, including serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum creatinine, and random blood sugar, were assessed at baseline and at six weeks. Adverse events were recorded. Data were expressed as mean ± standard error (SE), and statistical comparisons were performed using Student's t-test and chi-square test. **Results:** No statistically significant changes in hepatic enzymes, renal function, or metabolic parameters were observed within or between groups after six weeks of therapy ($p>0.05$). Adverse events were mild and self-limiting in both groups, with no serious hepatic or systemic toxicity reported. **Conclusion:** Oral itraconazole and terbinafine demonstrated comparable biochemical safety during six weeks of therapy. Routine biochemical monitoring remains advisable during systemic antifungal treatment.

INTRODUCTION: Superficial dermatophytosis is commonly treated with systemic antifungal agents when topical therapy is inadequate or when extensive disease is present. Oral itraconazole and terbinafine remain among the most frequently prescribed agents for moderate-to-severe infections. Although both drugs are considered effective, concerns regarding biochemical safety profile and adverse effects necessitate careful monitoring during therapy [1, 2, 3].

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Terbinafine, an allylamine antifungal, undergoes extensive hepatic metabolism and has been associated with rare but clinically significant hepatotoxicity [4]. Elevation of serum transaminases and, in uncommon cases, severe hepatic injury have been reported during systemic administration. Itraconazole, a triazole antifungal, inhibits cytochrome P450-dependent enzymes and may alter hepatic enzyme activity due to its metabolic profile and drug–drug interaction potential [5, 6].

Given their metabolism through hepatic pathways, periodic assessment of liver function during treatment is recommended. In addition to hepatic considerations, systemic antifungal therapy may influence metabolic parameters such as renal function and glycaemic status, particularly in

patients with predisposing conditions. Although significant toxicity is uncommon with short-term therapy, pharmacovigilance remains essential to ensure rational and safe prescribing practices [7, 8].

Most comparative studies evaluating itraconazole and terbinafine have primarily focused on clinical efficacy and mycological clearance. However, limited prospective data directly comparing their biochemical safety profiles under routine clinical conditions are available. In the context of increasing systemic antifungal use, the evaluation of biochemical safety parameters assumes clinical relevance.

The present prospective comparative study was therefore undertaken to evaluate and compare the biochemical safety profile of oral itraconazole and terbinafine in patients with superficial dermatophytosis.

MATERIALS AND METHODS: This prospective comparative observational study was conducted in the Department of Pharmacology in collaboration with the Department of Dermatology at JLN Medical College, Ajmer, Rajasthan, India, from September 2023 to December 2024. A total of 180 adult patients (≥18 years) with clinically diagnosed superficial dermatophytosis were included in the study. KOH microscopy was performed to support the diagnosis in all patients at baseline; however, clinical diagnosis was considered the primary basis for inclusion. Patients were allocated into two treatment groups of 90 participants each based on routine clinical prescribing practices. No formal randomization or allocation concealment was performed.

Patients fulfilling the inclusion criteria, including age ≥18 years, clinical diagnosis of superficial dermatophytosis, KOH examination performed to support diagnosis, and willingness to provide written informed consent, were enrolled. Patients with pre-existing hepatic, renal, or cardiovascular disorders, pregnancy or lactation, known hypersensitivity to azole or allylamine antifungal agents, immunocompromised status, or those unwilling to complete follow-up were excluded from the study. Uniform inclusion and exclusion criteria were applied to ensure baseline comparability between the two groups.

Patients in Group A received oral itraconazole 100 mg twice daily, while those in Group B received oral terbinafine 250 mg once daily. Both treatments were administered for a duration of six weeks using generic formulations. All patients in both groups received concomitant topical therapy with clotrimazole cream as part of standard treatment. The use of topical antifungal therapy was uniform across both groups.

Biochemical safety was assessed by evaluating biochemical parameters at baseline and after six weeks of therapy. The parameters included serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum creatinine, and random blood sugar (RBS). All laboratory investigations were carried out using standard institutional protocols. Adverse drug reactions were monitored throughout the study period and recorded based on clinical presentation.

The primary outcome measure was the change in hepatic and metabolic biochemical parameters from baseline to six weeks. The secondary outcome measure was the incidence and pattern of adverse drug reactions.

Continuous variables were expressed as mean ± standard error (SE). Within-group comparisons were performed using the paired Student's t-test, while between-group comparisons were analysed using the unpaired Student's t-test. Categorical variables were analysed using the chi-square test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using appropriate software as per institutional guidelines.

All patients were followed up at baseline and at six weeks. Treatment adherence was assessed through patient self-reporting and follow-up visits.

Ethical Considerations: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the guidelines of the Indian Council of Medical Research (ICMR). Ethical approval was obtained from the Institutional Ethics Committee of JLN Medical College, Ajmer (Approval No: 2429/Acad-II/MCA/2023-(168). Written informed consent was obtained from all participants before enrolment.

The study was conducted according to a predefined protocol that specified the inclusion and exclusion criteria, treatment regimens, duration of therapy, and outcome measures before initiation of the study. As this was a prospective observational study conducted in a routine clinical setting, formal clinical trial registration was not performed.

Treatment adherence was ensured through patient counselling at initiation of therapy and reinforcement during follow-up visits. Patients were followed up at baseline and at six weeks, and adherence was assessed based on patient self-reporting and confirmation during follow-up visits.

RESULTS: A total of 180 patients were enrolled in the study and were assigned to two treatment groups, with 90 patients in Group A (itraconazole) and 90 patients in Group B (terbinafine), based on routine clinical prescribing practices. All patients completed the six-week treatment period and were included in the final analysis.

The baseline demographic characteristics and clinical severity parameters were comparable between the two groups. The mean age was 36.08 ± 1.24 years in Group A and 36.67 ± 1.39 years in Group B, with no statistically significant difference ($p = 0.754$). Male predominance was observed in both groups (65.6% in Group A and 72.2% in Group B), and the difference was not statistically significant ($p = 0.336$). Other baseline parameters, including marital status, family history, and contact history, were also comparable between the groups ($p > 0.05$) **Table 1.**

TABLE 1: BASELINE CHARACTERISTICS OF STUDY POPULATION

Parameter	Group A	Group B	P-value
Age (Mean ± SE)	36.08±1.24	36.67±1.39	0.754
Male (%)	65.6	72.2	0.336
Married (%)	83	84	0.839
Family History (%)	66	56	0.169
Contact History (%)	56	61	0.449

Biochemical parameters were assessed at baseline and after six weeks of therapy. No statistically significant changes were observed within either group or between the two groups ($p > 0.05$ for all comparisons). In Group A, SGOT levels increased from 21.80 ± 0.99 U/L at baseline to 23.77 ± 1.24 U/L, while in Group B, they increased from 21.04 ± 1.02 U/L to 23.22 ± 0.95 U/L. Similarly, SGPT levels increased from 23.47 ± 0.92 U/L to 26.87 ± 0.71 U/L in Group A and from 22.72 ± 0.92 U/L to 23.50 ± 0.62 U/L in Group B.

Serum creatinine levels remained stable, with values changing from 0.80 ± 0.02 mg/dL to 0.86 ± 0.03 mg/dL in Group A and from 0.87 ± 0.02 mg/dL to 0.90 ± 0.02 mg/dL in Group B. Random blood sugar levels also showed no statistically significant variation, changing from 105.57 ± 2.68 mg/dL to 106.11 ± 2.13 mg/dL in Group A and from 110.62 ± 3.23 mg/dL to 111.66 ± 2.14 mg/dL in Group B. All biochemical parameters remained within institutional reference limits throughout the study period **Table 2.**

TABLE 2: COMPARISON OF BIOCHEMICAL PARAMETERS BETWEEN ITRACONAZOLE AND TERBINAFINE GROUPS

Parameter	Group A Baseline (Mean ± SE)	Group A 6 weeks (Mean ± SE)	p-value (within A)	Group B Baseline (Mean ± SE)	Group B 6 weeks (Mean ± SE)	p-value (within B)	p-value (between groups)
SGOT	21.80 ± 0.99	23.77 ± 1.24	0.598	21.04 ± 1.02	23.22 ± 0.95	0.7673	>0.05
SGPT	23.47 ± 0.92	26.87 ± 0.71	0.7400	22.72 ± 0.92	23.50 ± 0.62	0.5434	>0.05
Creatinine	0.80 ± 0.02	0.86 ± 0.03	0.4311	0.87 ± 0.02	0.90 ± 0.02	0.3910	>0.05
RBS	105.57 ± 2.68	106.11 ± 2.13	0.2328	110.62 ± 3.23	111.66 ± 2.14	0.1374	>0.05

Data are expressed as mean ± standard error (SE). Within-group comparisons were performed using paired Student's t-test and between-group comparisons using unpaired Student's t-test. No statistically significant differences were observed ($p > 0.05$). The institutional reference ranges were as follows: SGOT (5–40 U/L), SGPT (5–40 U/L), serum creatinine (0.6–1.2 mg/dL), and random blood sugar (70–140 mg/dL).

The majority of patients (90.55%) did not report any adverse effects. Mild and self-limiting adverse events, including headache, constipation, diarrhea, nausea, and rash, were observed in a small proportion of patients. No serious adverse events were recorded. The distribution of adverse drug reactions was comparable between Group A and Group B, with no statistically significant difference (Chi-square test, p = 0.91) **Table 3.**

TABLE 3: DISTRIBUTION OF ADVERSE DRUG REACTIONS

Adverse Effect	Group A (n=90)	Group B (n=90)	Total (n=180)	Percentage (%)
No complaint	82	81	163	90.55
Headache	2	1	3	1.66
Constipation	2	3	5	2.77
Diarrhea	2	2	4	2.22
Nausea	2	2	4	2.22
Rash	0	1	1	0.55
Total	90	90	180	100

As a supportive finding, KOH positivity decreased in both groups after six weeks of therapy, with no statistically significant difference between the groups (p = 0.137).

DISCUSSION: The present prospective study evaluated and compared the biochemical safety of oral itraconazole and terbinafine during six weeks of therapy in patients with superficial dermatophytosis. Both antifungal agents were well tolerated, and no clinically meaningful alterations in liver enzymes, renal function, or glycaemic parameters were observed. Topical antifungal therapy with clotrimazole was uniformly administered in both groups, minimizing its potential influence on comparative outcomes.

Systemic antifungal therapy is often associated with concerns regarding hepatotoxicity because both itraconazole and terbinafine undergo hepatic metabolism. Terbinafine is extensively metabolized in the liver and has been associated with transient elevation of serum transaminases in a small proportion of patients, although clinically significant hepatic injury remains rare [1, 2, 3]. Post-marketing surveillance data suggest that severe hepatotoxic reactions are uncommon and usually reversible after drug discontinuation [4].

Itraconazole inhibits cytochrome P450–dependent 14-α-demethylase and may alter hepatic enzyme activity due to its metabolic pathway and interaction potential [5, 6]. Mild elevations in transaminases have been described during therapy, particularly in patients receiving prolonged treatment or concomitant hepatotoxic drugs [7]. However, most short-duration clinical studies have reported minimal clinically relevant biochemical changes when itraconazole is used at standard doses [8, 9].

The absence of significant hepatic enzyme elevation in the present study is consistent with previously published prospective evaluations of short-term antifungal therapy. These findings suggest that, in otherwise healthy adults without baseline hepatic dysfunction, six-week administration of either agent is unlikely to produce clinically significant hepatotoxicity [10, 11, 12].

Renal function and random blood sugar levels remained stable throughout therapy. Although nephrotoxicity is not a commonly reported adverse effect of these agents, routine biochemical monitoring is often recommended in clinical practice [13, 14]. The present findings reinforce the safety of both drugs with respect to metabolic and renal parameters under standard treatment conditions. However, the assessment of metabolic safety in the present study was limited to serum creatinine and random blood sugar, and a more comprehensive metabolic evaluation, including parameters such as lipid profile or HbA1c, was not performed.

Adverse events observed were mild and self-limiting, consistent with the known tolerability profile of both itraconazole and terbinafine [15, 16]. No serious hepatic or systemic toxicity was recorded in this study. Detailed efficacy analysis was beyond the scope of the present study, as the primary objective was to evaluate biochemical safety.

The present study has certain limitations that should be acknowledged. The duration of therapy was limited to six weeks, and long-term hepatic outcomes were not evaluated. Patients with pre-existing hepatic or renal impairment were excluded; therefore, the findings may not be generalizable to high-risk populations. Additionally, pharmacokinetic measurements and serum drug concentration assessments were not performed.

As this was a prospective observational study, treatment allocation was not randomized, which may introduce potential selection bias. Furthermore, detailed disease-related baseline variables such as duration of illness, body surface area involvement, prior antifungal exposure, comorbidities, and concurrent medication use were not assessed. Baseline demographic characteristics were comparable between the groups; however, detailed disease-related variables were not assessed.

CONCLUSION: Oral itraconazole and terbinafine demonstrated comparable biochemical safety during six weeks of therapy in patients with superficial dermatophytosis. Within the limits of the study design, both agents appear safe when prescribed at standard doses with appropriate baseline assessment and monitoring.

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CONFLICTS OF INTEREST: Nil

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