ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 3, May - 2023, Page No. : 512 - 517

Comparative study of effectiveness and safety of capsule super bioavailable itraconazole and Conventional itraconazole in the management of dermatophytosis in India.

[1]Dr. Suvir M, Department of Dermatology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Mangalore

[2]Dr. Pallavi N swami, Department of Dermatology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Mangalore

[3]Dr. Priya Hegde, Department of Dermatology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Mangalore

Corresponding Author: Dr. Suvir M, Department of Dermatology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Mangalore

How to citation this article: Dr. Suvir M, Dr. Pallavi N Swami, Dr. Priya Hegde "Comparative study of effectiveness and safety of capsule super bioavailable itraconazole and Conventional itraconazole in the management of dermatophytosis in India.", IJMACR- May - 2023, Volume – 6, Issue - 3, P. No. 512 – 517.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: A novel itraconazole formulation, super bioavailable itraconazole (SBITZ), was recently announced in India, claiming to address all of the pharmacokinetic problems associated with conventional itraconazole (CITZ). The current retrospective data analysis was performed to compare the efficacy and safety of super bioavailable itraconazole to conventional itraconazole in the treatment of dermatophytosis in Indian patients.

Materials and methods

Patients and Methods: This was an open-label, randomized, double-arm clinical study in Which 100 patients (>18years) of either gender with tinea cruris or tinea faciei or tinea corporis attending the dermatology OPD at tertiary hospital in Mangalore. Duration of study was from January 2022 to April 2022. The study was divided into two parts, the first part comprising a treatment period of 4 weeks and the second part an observation period for recurrence, comprised of another 4 weeks, thus making an entire study duration of 8 weeks.

Results: From the 100 patients included in this study, 80 (42 patients in the CITZ group and 38 patients in the SBITZ group) were included in the final study. At week 4, 17 patients (40.47%) and 24 patients (63.15%) had achieved complete cure ($p<0.05$), but 25 patients (59.5%) and 31 patients (81.5%) had achieved mycological cure ($p=0.12$), in the CITZ and SBITZ groups, respectively. During the follow up period,

recurrence was seen in 2/42 and 2/34 completely cured patients in the CITZ and SBITZ groups, respectively (p=0.16). A significant difference was also found in resolution of symptoms as well as lesions of dermatophytosis in the SBITZ group (p<0.05). It was determined that both therapies were secure and well-tolerated.

Conclusion: In view of real-world evidence on efficacy and safety, SBITZ should be evaluated as a viable therapeutic option for efficiently controlling the existing dermatophytosis problem in India. From the findings of the present study, super bioavailable itraconazole was more effective with similar

Safety profile as compared to conventional itraconazole in the treatment of dermatophytosis.

Keywords: Super Bioavailable Itraconazole, Safety, Conventional Itraconazole, Effectiveness, Dermatophytosis.

Introduction:

Dermatophytosis are majority of the cases attending dermatology outpatient department across India, presenting with multiple-site lesions, extensive skin lesions, unusually large lesions, involvement of unusual sites such as the face and genitals, ring-within-ring lesions, and other topical corticosteroid-modified lesions, making diagnosis and treatment difficult. In addition, unlike many other dermatological disorders, individuals have had persistent and repeated recurrences of the disease. [1]

Super bioavailable itraconazole have been claimed to have the benefits of increased bioavailability, no food interaction, less inter-subject variability, no reduction in absorption with concomitant use of antacids not seen with other gastric acid lowering agents, which are seen with conventional itraconazole[2]As a result, dermatologists in India are depending on a variety of experience-based therapy techniques, such as extended treatment duration, higher antifungal dosages, and other medicines that have not been approved for the routine management of dermatophytosis.[2,3]

Itraconazole (ITZ) is a systemic antifungal drug used in the treatment of dermatophytosis owing to its excellent potency compared to other systemic antifungal drugs.[4] ITZ is an orally available triazole antifungal drug and is considered to be a first-line drug for the treatment of tinea corporis and cruris.

However, because of its inherent pharmacokinetic characteristics, ITZ shows unpredictable absorption patterns. Being a weak base molecule, it requires an acidic ph. For its dissolution; therefore, it is recommended to be taken with acidic beverages. Since its absorption is lower in the fasting state, ITZ has to be taken with meals, especially fatty meals, to achieve optimal absorption and bioavailability. Concomitant use of gastric acid-lowering agents such as proton pump inhibitors (ppis) reduces its absorption, leading to a further reduction in bioavailability. [7] In a real-world setting, it is difficult to ensure all of these factors to obtain the optimum bioavailability of ITZ.

Moreover, even under ideal conditions, the optimal level of gastric acid secretion cannot be guaranteed as it is dependent on various factors, such as the circadian rhythm, stress levels, and eating and sleeping patterns.[8] Because of these factors, the bioavailability of conventional itraconazole (CITZ) is only up to 55%, and this, too, fluctuates widely depending on the amount of gastric acid secretion, which leads to wide interpatient variability [7,9] and variations in the clinical response in patients. In this scenario, the intrinsic pharmacokinetic

properties of ITZ may play a major role in its increased dose and duration in the treatment of dermatophytosis.

Recently, a new oral version of ITZ called super bioavailable itraconazole (SBITZ) was launched in India in 2020 as a 50 mg pill, which is bioequivalent to (CITZ) 100 mg. It is approved in several countries for the treatment of invasive mycoses such as aspergillosis and candidiasis. [10] It combines an ITZ solid dispersion in a non-pellet formulation with a ph-dependent polymeric matrix, hydroxypropyl methylcellulose phthalate (HPMCP), which improves dissolving and intestinal absorption [11] giving it greater bioavailability than CITZ.

SBITZ has been extensively researched in different indications [10] However, clinical data on its use in superficial fungal infections is limited. There are currently no Indian clinical trials comparing its efficacy and safety in dermatophytosis to CITZ. As a result, the current clinical research was designed to compare the efficacy and safety of SBITZ to CITZ in patients with dermatophytosis.

Patients and Methods

Study Participants:

A total of 100 adult patients (≥18 years of age) of either gender attending the dermatology outpatient's department at a tertiary hospital in Mangalore, India, January 2022 to June 2022.

Clinically and mycologically diagnosed cases of tinea cruris and/or tinea corporis and/or tinea faciei, were included in the study. Patients with any significant medical illness, such as diabetes, cardiac disease, or immunocompromised conditions, that would have affected clinical outcomes, and female patients who were pregnant or lactating, were excluded from the study according to the investigator's discretion. The study was conducted in compliance with the protocol approved by the Ethics Committee of the medical college, Mangalore where in the study was conducted. Written informed consent was obtained from all patients prior to their participation in the study.

Study Design and Treatment:

This was an open-label, randomized, double-arm clinical trial, conducted to compare the effectiveness and safety of SBITZ capsules and CITZ capsules in the management of tinea corporis, tinea cruris, and tinea faciei in 2 groups along with luliconazole cream in the morning and liquid paraffin in the night. Eligible patients were randomized into two groups to receive either itraconazole, 100 mg twice a day (CITZ), or super bioavailable itraconazole, 50 mg twice a day (SBITZ), at the discretion of the treating physician and at approved dosages.

Included patient's demographics and baseline clinical features, including site of lesion, extent of lesion, duration of current illness, clinical symptoms and signs score, treatment history, and number of previous episodes, were recorded at baseline (day 0). All patients' diagnoses were confirmed on direct microscopy under 10% potassium hydroxide examination (KOH mount), which was repeated at the end of the treatment period (4 weeks). Upon confirmation by KOH mount, on visit 2 (day 1), all of the patients were either prescribed CITZ or SBITZ. The study was divided into two parts, the first part comprising the treatment period, of 4 weeks, and the second part an observation period comprising another 4 weeks, thus making an entire study duration of 8 weeks. During the treatment period, patients were followed up as per routine protocol, and clinical assessment data were collected on visit 2 (day 1), visit 3 (day 29±2). Following this treatment period, patients with complete cure were not prescribed any antifungal medication,

while the rest of the patients with improvement were allowed to take antifungal medication at the discretion of the treating physician. All the patients with complete cure were contacted by telephone regarding any recurrence of disease at day 57±2. The complete study design is shown in Figure 1.

The patients were categorized as naïve, chronic, or recurrent, depending upon the history of clinical presentation. Naive cases were defined as patients who had not been previously exposed to a particular infection with a given disease or treatment for that disease. Chronic cases were patients who had suffered from the disease for more than 6 months to 1 year, with or without recurrence, in spite of being adequately treated. Recurrent cases were defined as patients who encountered reoccurrence of the disease (lesions) within a few weeks (<6 weeks) after completion of the treatment.[1]

Outcome Assessments

The primary endpoint of the study was the comparison of the percentage of patients achieving a complete cure (clinical cure plus mycological cure) at the end of treatment period from baseline. Clinical cure was defined as a combination of the absence of any signs and symptoms (total symptom score of 0) and the absence of the extent of lesions in terms of the body surface area (BSA). The total symptom score (TSS) comprised four symptoms: scaling, pruritus, erythema, margin continuity and elevation of the representative lesion. Each symptom was scored on a four-point Likert scale of 0–3, where 0 denotes the absence of a symptom and 3 denotes the maximum intensity of an individual symptom. The TSS was obtained by the summation of the individual signs and symptoms score at each time point (range 0–12). The extent of lesions in terms of BSA ranged from 0 to 3, where 0 corresponds to the absence of lesions, 1 to BSA involvement of <3%, 2 to BSA involvement of 3–10%, and 3 corresponds to BSA involvement of >10%. In addition, the investigator's global assessment of effectiveness and safety (IGA) graded on a four-point scale (0=poor, 1=satisfactory, 2=good, and 3=excellent) at visits 2, 3, and 4.

KOH Mount

Mycological cure was defined as a negative report on the KOH mount at week 4. A scraping of the skin was directly collected on to the slide. Potassium hydroxide 10% was added to the material, covered by a coverslip of fragile glass, and gently preheated before examination. Microscopic examination was performed with a direct light microscope to detect fungal spores or hyphae. The initial examination was carried out at lowpower magnification (×10) and later at higher magnification (×40). The secondary outcome measures included percentage change in mean TSS, BSA, and IGA from baseline to subsequent visits. The safety assessment was based on spontaneous adverse events (aes) reported by patients and clinicians throughout the study period (8 weeks).

Statistical Analysis

Baseline demographic and clinical characteristics were presented as numbers and percentages, and as means with standard deviations (sds). The primary and secondary effectiveness endpoints were summarized using descriptive statistics; frequencies were reported for categorical variables and means with SD. The difference in the proportion of patients with total signs and symptom scores

(Based on improvement criteria) was analyzed using the chi-squared test with a significance level of 0.05. The two groups were compared by Fisher's exact test. All

statistical analyses were performed using SPSS version 15 (SPSS, Chicago, IL, USA).

Results

Baseline Clinical Characteristics

Of the 100 patients enrolled in this study, 80 were included in the FAS. There were 42 patients in the CITZ group and 38 patients in the SBITZ group. A male predominance was seen in SBITZ group at 58% while female in CITZ group at 52%, respectively, with a mean± SD age of 40.9 ±11.3 vs 39.62±12.36 years, respectively in CITZ vs SBITZ (Table 1). All of the baseline characteristics are presented in Table 1. The patient distribution was homogeneous in both groups. In both groups, most patients were diagnosed with tinea cruris et corporis, with at least five lesions. About 24 % and 26% of the patients in both groups had already obtained treatment from the chemist, and topical steroid usage was seen in 19% and 13.1% of the patients in the CITZ and SBITZ groups, respectively.

Treatment Response

Effectiveness

At week 4, 17 patients (40.47%) (10 patients with chronic, 5 patients with recurrent, and 6 patients with naïve dermatophytosis) and 24 patients (63.1%) (12 patients with chronic, 6 patients with recurrent, and 7 patients with naïve dermatophytosis) achieved complete cure, whereas 25 patients (59.5%) and 31 patients (81.5%) achieved mycological cure in the CITZ and SBITZ groups, respectively. Clinical improvement in patients in the SBITZ and CITZ groups is shown in Figures 2 and 3 respectively. There was a statistically significant difference between the two groups in completely cured patients ($p<0.05$), whereas in mycologically cleared patients, no statistically significant difference was found ($p=0.18$). During the observation period, recurrence was seen in 2 out of 17 and 2 out of 24 completely cured patients in the CITZ and SBITZ groups, respectively ($P=0.20$). On subgroup analysis, similar results were obtained in chronic dermatophytosis: in the CITZ group, 10 out of 17 patients (58.8%) and in the SBITZ group 12 out of 18 patients (66.6%) achieved complete cure ($p=0.09$), whereas 15 (57.89%) and 16 (93.33%) patients, respectively, achieved mycological cure ($p<0.05$). Recurrence was seen in these groups of patients and in the recurrent dermatophytosis group, as shown in Table 2. The number of patients with improvement, for recurrent and naïve patients, is also shown in Table 2.

Improvement in Mean Scores

At week 4, the mean TSS of 9.83±1.6 was reduced to 1.55± 1.3 (86.2% reduction) in the CITZ group, while it was reduced from 9.40±1.42 to 0.67 ± 1.09 (95.4% reduction) in the SBITZ group. Both treatments were statistically significant in reducing TSS at the end of the visits ($p<0.05$) from baseline. Significant lesion clearance was also seen in both groups at both visits. At week 4, the mean BSA score reduced from 2.25 ± 0.67 to 0.34 ± 0.34 (78.4% reduction) in the CITZ group, compared to 0.34 ± 0.34 (96.2% reduction) in the SBITZ group. There were statistically significant differences in intergroup as well as intragroup comparisons ($p<0.05$). Similar results were obtained for mean IGA score (Table 3).

Adverse Events

A total of 3 aes were reported: 1 in the CITZ group and 2 in the SBITZ group. All Three patients in the had temporary, self-resolving gastrointestinal disturbances. No patient in the SBITZ group discontinued the treatment as a result of aes. All of the aes were mild to

moderate in nature. In general, all of the patients tolerated therapy very well.

Discussion

In the modern era of dermatophytosis, ITZ, along with topical therapy, is a valuable antifungal medicine, although its efficacy is restricted by its inherent pharmacokinetics. Factors that lead to varying therapeutic doses.[12] All of these factors are frequently overlooked in real-world clinical practise. When compared to older CITZ formulations, a newer formulation of SBITZ demonstrated more consistent attainment of therapeutic concentration. [13,14] There are a few clinical studies on SBITZ use in various conditions, but there is no clinical proof on dermatophytosis.

The findings of this study revealed that SBITZ was related with faster improvement and a higher full cure rate than CITZ. In the SBITZ group, 63.15% of patients achieved a complete cure, whereas the same was achieved by only 40.47% of the patients in the CITZ group. In a retrospective study by Mahajan et al published in 2021, 56% of the patients achieved complete clearance of their symptoms in the SBITZ group, whereas 34% achieved the same in the CITZ group ($p<0.05$).[15] From their results, the authors concluded that SBITZ was more effective than CITZ, with a similar safety profile, in the treatment of dermatophytosis. In addition, a retrospective cohort study by Ghate et al on SBITZ concluded that patients treated with SBITZ showed greater improvement in the clearance of symptoms as well as lesions in just 4 weeks.[16] In the same study, 51% of the patients achieved a complete cure. In the CLEAR (Clinical Assessment of Itraconazole in Dermatophytosis) study [17] on the effectiveness and safety of CITZ, about 70% of patients achieved clinical cure with CITZ. In all of the above studies, along with ITZ, a topical antifungal was also prescribed but in a study by Shenoy et al topical steroids were not used [23]. In our study, we have reported better and significant results with SBITZ than with CITZ with the use of a topical antifungal; however, an emollient was also used. Emollient use may improve barrier dysfunction and help to achieve better symptom resolution.

In our study, the mycological cure rate (based on KOH mount) was not statistically significant, with 81.5% of patients in the SBITZ group and 59.5.5% of patients in the CITZ group achieving a mycological cure. These results are not in line with other clinical trials comparing the efficacy and safety of SBITZ and CITZ in patients with onychomycosis. [10] Recurrence was seen in both groups, with no statistically significant difference. On subgroup analysis, similar results were obtained for chronic dermatophytosis, where patients in the SBITZ group showed better improvement. In a report published in 2021, SBITZ was found to be effective in the management of naïve, recurrent, and chronic dermatophytosis. [16] Moreover, SBITZ continued to be associated with a decrease in TSS during the treatment period, as well as with an improvement in overall disease severity, as measured by BSA involvement. In terms of IGA, as well, SBITZ demonstrated remarkably better results.

Apart from a complete cure, significant percentage reductions were seen in all mean TSS, BSA, and IGA scores at weeks 4 for SBITZ. In the SBITZ group, a TSS reduction was seen in 93% of patients at the end of 4 weeks. Similar results were also seen in another study, [16] where 89.8% of patients achieved a reduction in TSS. We also noticed a reduction in BSA involvement in 94.26% of the patients in the SBITZ group, which is

similar to the previous study, where 81% of patients achieved such a reduction.16 This indicates that SBITZ is effective in relieving the symptoms as well as the lesions of dermatophytosis. These better cure rates in SBITZ can be attributed to its pharmacokinetic advantages compared to CITZ. ITZ is a weak base molecule with a highly variable absorption pattern, leading to wide fluctuations in its blood concentration, [18] and hence the bioavailability of CITZ is only around 55%. [9,19] To generate an optimal clinical effect, a drug's absorption and thus bioavailability must be high, with minimum intraindividual and interindividual variability. SBITZ is a solid dispersion of ITZ in a uniform non-pellet formulation with a ph-dependent polymeric matrix (HPMCP), which improves dissolution and intestinal absorption.[11] As a result, SBITZ is regularly released and absorbable throughout the small intestine, which is the primary location of ITZ absorption. [11,20] ensuring increased bioavailability and less intraindividual and interindividual variability. [21]

In the treatment of dermatophytosis, sebum content is one of the most critical indicators of the outcome of any antifungal medication. Because ITZ is a lipophilic medication, its excretion in sebum and concentration in the stratum corneum are important, especially in people with dermatophytosis. In an unreported Indian study, the sebum concentrations of SBITZ and CITZ were evaluated in healthy volunteers, and it was discovered that SBITZ had an 11.6% higher sebum content than CITZ after only 7 days (p=0.01). [22] Because the SBITZ group had a higher mycological cure rate in our trial, a higher medication concentration at the target site may aid in the complete eradication of fungus from the lesions. As a result, the increased concentration of sebum obtained in our study may be responsible for the SBITZ group's improved performance in many examined criteria.

The therapy was well tolerated by all patients in both groups, and no significant adverse events occurred. Both treatments were found to be safe and tolerable. [3] adverse events were reported, all of which were minor. Due to aes, only one patient in the CITZ group terminated treatment. The treatment time in this clinical trial was just 4 weeks, and a longer duration of therapy may be required in the future to prevent recurrence. The study's biggest weakness is its small sample size. Small sample size. Hence, long-term clinical trials with a larger population are warranted to validate the results of the present study.

Conclusion

Patients treated with SBITZ demonstrated higher improvement in lesion clearance compared to those treated with placebo in naive, recurrent, and chronic patients, allowing its inclusion in the care of all kinds of dermatophytosis. It is risk-free and well-tolerated. In view of real-world evidence on efficacy and safety, SBITZ should be evaluated as a viable therapeutic option for efficiently controlling the existing dermatophytosis threat in India.

Flow chart 1: Study design.

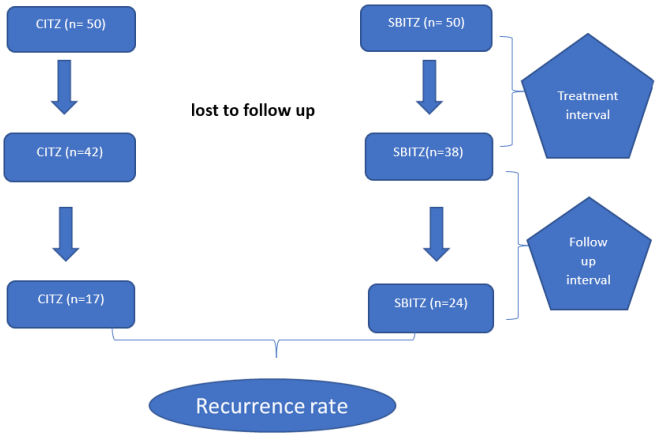

Table 1: Baseline demographic characteristics

parameters	Conventional itraconazole	Super bioavailable itraconazole	P value
N	42	38	
Males ,n (%)	20 (48%)	22(58%)	0.15
Females, n (%)	22 (52%)	16 (42%)	0.19
Age (years) mean ± SD	40.9± 11.3	39.62±12.36	0.38
Distribution of anatomical sites			
Multisite , n (%) Tinea cruris et corporis Tinea cruris Tinea corporis Tinea faciei	10(23.8%) 25(59.5%) 10 (23%) 5(11%) 2(4.8%)	15(39%) 22(57%) 12(31.5%) 2(5.2%) 2(5.2%)	0.42 0.19 0.8 0.9 0.19
No. of lesions			
1-2 lesions , n (%) 3-4 lesions , n (%) ≥ 5 lesions , n (%)	4 (9.5%) 10 (23%) 28 (66.6%)	6 (15.7%) 12 (31.5%) 20 (52.6%)	0.41 0.9 0.4

Table 2: Effectiveness Evaluation in Chronic, Recurrent and Naïve Patients

Naïve, n (%) Recurrences ,n (%) Chronic, n (%)	15 (36%) 10 (24%) 17 (40.4%)	10 (26.3%) 10 (26.3%) 18 (47.3%)	0.58 0.88 0.9
Previous treatments			
Chemist, n (%) Dermatologist , n (%) Topical steroids ,n (%)	15 (36%) 10 (24%) 17 (40.4%)	10 (26.3%) 10 (26.3%) 18 (47.3%)	0.58 0.88 0.9
Effectiveness evaluation score			
Total symptom score (TSS), mean ±SD Body surface area (BSS), mean ± SD Investigators global assessment score IGA, mean±SD	9.83±1.6 2.25±0.67 2.68±0.78	9.40±1.42 1.98±0.78 2.99±0.6	0.44 0.09 0.35

Table 3: Mean Scores at Baseline and Week 4 in Both Treatment Groups

Parameters	CITZ	SBITZ	P VALUE
Effectiveness evaluation	42	38	
Complete cure	17	24	0.02*
Mycological cure	25	31	0.18
Recurrence	2	2	0.20
chronic dermatophytosis	17	18	
complete cure	10	12	0.09
Mycological cure	15	16	0.03*
Recurrence	1	1	0.12
Recurrent dermatophytosis	10	10	
complete cure	5	6	0.76
Mycological cure	6	8	0.75
Recurrence	1	0	
naïve dermatophytosis	15	10	
Complete cure	6	7	0.34
Mycological cure	9	9	0.14
Recurrence	0	0	

Table 4 : Mean Scores at Baseline and Week 4 in Both Treatment Groups

Parameters	Conventional itraconazole	Super bioavailable itraconazole	P value
TSS			
Baseline Day 28	9.83±1.6 1.55 1.3	9.40±1.42 0.67 1.09	0.33 0.01*
BSA			
Baseline Day 28	2.25±0.67 0.34 0.34	1.98±0.78 0.34 0.34	0.07 0.02*
IGA			
Baseline Day 28	2.68±0.78 0.65 0.32	2.99±0.6 0.29 0.23	0.2 0.04*

Fig 1: Showing post treatment with CITZ and

Fig 2 : Showing post treatment with SBITZ

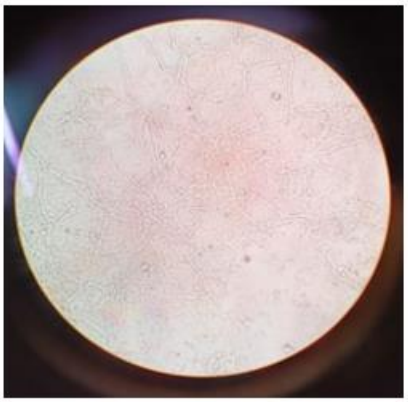

Fig 3 : Showing KOH confirmation.

References

1. Rajagopalan M, Inamadar A, Mittal A, et al. Expert consensus on the management of dermatophytosis in India (ECTODERM India). BMC Dermatol. 2018;18(1):6. Doi:10.1186/s12895-018-0073-1

2. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: an appraisal. Indian J Dermatol. 2017;62 (3):227–236.

3. 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:10.4103/2229-5178.178100

4. Das S, De A, Saha R, et al. The current Indian epidemic of dermatophytosis: a study on causative agents and sensitivity patterns. Indian J Dermatol. 2020;65(2):118–122. Doi:10.4103/ijd.IJD_203_19

5. Boonk W, de Geer D, de Kreek E, Remme J, van Huystee B. Itraconazole in the treatment of tinea corporis and tinea cruris: comparison of two treatment schedules. Mycoses. 1998;41(11– 12):509–514. Doi:10.1111/j.1439-0507.1998.tb00714.

6. Rengasamy M, Shenoy MM, Dogra S, et al. Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) Task Force against Recalcitrant Tinea (ITART) Consensus on the Management of Glabrous Tinea (INTACT). Indian Dermatol Online J. 2020;11(4):502–519.

7. Lindsay J, Mudge S, Thompson GR. Effects of food and omeprazole on a novel formulation of super bioavailability itraconazole in healthy subjects. Antimicrob Agents Chemother. 2018;62(12): e01723–18. Doi:10.1128/AAC.01723-18

8. Vaughn B, Rotolo S, Roth H. Circadian rhythm and sleep influences on digestive physiology and disorders. Chrono Physiol Ther. 2014;4:67–77. Doi:10.2147/CPT.S44806

9. SP0RANOX® (itraconazole) capsule [prescribing information]. Raritan, NJ: Ortho-mcneil-Janssen Pharmaceuticals, Inc; 2018.

10. LOZANOC® (itraconazole 50 mg) capsule [prescribing information]. Salisbury South, SA: Mayne Pharma International Pty Ltd; 2020.

11. Abuhelwa AY, Foster DJ, Mudge S, Hayes D, Upton RN. Population pharmacokinetic modeling of itraconazole and hydroxyitraconazole for oral SUBA-itraconazole and sporanox capsule formulations in healthy subjects in fed and fasted states. Antimicrob Agents Chemother. 2015;59(9):5681–5696. Doi:10.1128/AAC.00973-15.

12. Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics. J Antimicrob Chemother. 2005;56(Suppl 1):i17– i22. Doi:10.1093/jac/dki220

13. Lindsay J, Sandaradura I, Wong K, et al. Serum levels, safety and tolerability of new formulation SUBA-itraconazole prophylaxis in patients with haematological malignancy or undergoing allogeneic
Stem cell transplantation. J Antimicrob Chemother. 2017;72(12): 3414–3419. Doi:10.1093/jac/dkx295

14. Nield B, Larsen SR, van Hal SJ. Clinical experience with new formulation SUBA®-itraconazole for prophylaxis in patients undergoing stem cell transplantation or treatment for haematological malignancies. J Antimicrob Chemother. 2019;74(10):3049–3055. Doi:10.1093/jac/dkz303

15. Mahajan H, Dhoot D, Deshmukh G, Barkate H. Comparative clinical effectiveness and safety of super bioavailable itraconazole and conventional itraconazole in management of dermatophytosis: a retrospective data

analysis. Int J Res Dermatol. 2021;7:388–394. Doi:10.18203/ issn.2455-4529.intjresdermatol20211427

16. Ghate S, Dhoot D, Mahajan H, Barkate H. Clinical assessment of super bioavailable Itraconazole 50 mg in dermatophytosis (Clear 50). IP Indian J Clin Exp Dermatol. 2021;7(2):125–129.

17. Mahajan H, Dhoot D, Barkate H. Clinical assessment of itraconazole in dermatophytosis (CLEAR Study): a retrospective evaluation. Int J Sci Stud. 2020;8(2):1–5.

18. Gintjee TJ, Donnelley MA, Thompson GR. Aspiring antifungals: review of current antifungal pipeline developments. J Fungi (Basel). 2020;6(1):28.

19. Brouwers J, Geboers S, Mols R, Tack J, Augustijns P. Gastrointestinal behavior of itraconazole in humans - Part 1: supersaturation from a solid dispersion and a cyclodextrin-based solution. Int J Pharm. 2017;525 (1):211–217. Doi:10.1016/j.ijpharm.2017.04.029

20. Abuhelwa AY, Mudge S, Hayes D, Upton RN, Foster DJ. Population in vitro-in vivo correlation model linking gastrointestinal transit time, ph, and pharmacokinetics: itraconazole as a model drug. Pharm Res. 2016;33(7):1782–1794.

21. Cauwenbergh G, Degreef H, Heykants J, Woestenborghs R, Van Rooy P, Haeverans K. Pharmacokinetic profile of orally administered itraconazole in human skin. J Am Acad Dermatol. 1988;18 (2):263–268.

22. Harshal M, Gaurav J, Dhiraj D, Gaurav D, Hanmant B. Serum and sebum pharmacokinetics evaluation of a novel formulation of itraconazole in healthy volunteers. Indian J Drugs Dermatol. 2021.

23. Manjunath Shenoy et al , An open label An Open-Label, Randomized, Double-Arm Clinical Trial to Compare the Effectiveness and Safety of Super Bioavailable Itraconazole Capsules and Itraconazole Capsules in the Management of Dermatophytosis in India. Clinical cosmetic and investigational dermatology 2021:14 1367-76