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ORIGINAL RESEARCH

Pharmacokinetic and clinical comparison of super-bioavailable itraconazole and conventional itraconazole at different dosing in dermatophytosis

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Abstract

Background: Due to changing face of dermatophytosis in India, many dermatologists practice different dosing patterns of itraconazole (ITZ). Recently, a new form of ITZ, super-bioavailable ITZ (SBITZ), has been commercialized to overcome the pharmacokinetic challenges of conventional ITZ (CITZ). Serum and sebum concentration of ITZ plays an important role in the management of dermatophytosis. Hence, the current study compares the rate and extent of serum and sebum concentration of SBITZ and CITZ at different dosing to determine their efficacy and safety in patients with dermatophytosis.

Methods: This was an open-label, randomized, four-arm study including 40 adult patients diagnosed with glabrous tinea who were randomized equally into four groups to receive either CITZ-100-BD or CITZ-200-OD (2×100 mg capsules) or SBITZ-130-OD or SBITZ-100-OD (2×SBITZ-50 mg capsules) for 4 weeks. Serum and sebum samples were analysed at different time intervals along with clinical efficacy and safety.

Results: For serum concentration, on day 28, the arithmetic mean and standard deviation (SD) for CITZ-100-BD, CITZ-200-OD, SB-130-OD and SB100-OD were 1262±233.5 ng/mL, 1704±261.6 ng/mL, 1770±268.9 ng/mL and 1520±231.7 ng/mL, respectively, which was statistically significant for OD dosing of ITZ/SBITZ over CITZ-100-BD. Similarly, for sebum concentration, the arithmetic mean and SD for CITZ-100-BD, CITZ-200-OD, SB-130-OD and SB-100-OD were 1042±163.45 ng/mg, 1423±192.46 ng/mg, 1534±227.55 ng/mg and 1107±182.35 ng/mg, respectively, which was statistically significant for SB-130-OD and CITZ-200-OD over CITZ-100-BD and SBITZ-100-OD dosing. No significant difference was noted between SBITZ-130 and CITZ-200 (p=0.25). Only two patients achieved complete cure in the SBITZ-130 group, whereas no patients achieved the same in other groups (p=0.47). All the dosages were very well tolerated with only 12 adverse events reported by ten patients in all groups.

Conclusion: All formulations achieved desired serum and sebum concentrations required for efficacy in dermatophytosis, but SB 130 mg OD and CITZ 200 mg OD were statistically significant than other ITZ doses in achieving sebum concentration. Additionally, SBITZ 130 mg OD was bioequivalent to CITZ 200 mg OD and achieved similar results to those of CITZ 200 mg OD but at 35% lower drug concentrations.

Keywords: dermatophytosis, itraconazole, sebum concentration, serum concentration, super-bioavailable itraconazole.

Citation

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Introduction

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. Although itraconazole (ITZ) is the most commonly prescribed systemic antifungal due to its potency,[1] 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.[2] In one study on serum concentration of ITZ by Wiederhold et al.,[3] only 55.4% of patients were found to have serum concentrations above 500 ng/mL, a reference level set in invasive fungal infections.[4] Additionally, it was found that sebum levels of ITZ were ten times as high as the corresponding peak plasma levels[5]; therefore, sebum concentrations of ITZ become more important when used for the management of dermatophytosis.[6]

A new formulation, super-bioavailable ITZ (SBITZ) has been recently launched in many countries as 50 mg capsules[7] and in the United States as 65 mg capsules.[8] 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).[9] 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.[10,11] Additionally, prescription patterns vary highly for the same concentration of drug like CITZ 100 mg twice-daily (BD) or CITZ 200 mg once-daily (OD) or SBITZ 130 mg OD or 100 mg OD, though due to the non-linear pharmacokinetics profile of ITZ, OD dosing is recommended for ITZ over BD dosing.

Considering the importance of sebum concentration of ITZ in the management of dermatophytosis, as mentioned earlier, evaluating the same for SBITZ also becomes critical. There is paucity of such data for different strengths of SBITZ. Hence, this study was planned with the aim of comparing the rate and extent of serum and sebum concentrations of SBITZ and CITZ at different dosing and to determine their efficacy and safety in patients with dermatophytosis.

Methods

The study was conducted at Scarlet Dermatology Clinic and the School of Pharmaceutical Education and Research, Jamia Hamdard Institute, New Delhi, India, during May to June, 2022. Trial registration number – CTRI/2022/04/042183.

Study participants

A total of 40 patients with glabrous tinea (dermatophytosis) were enrolled in the study. Pre-enrolment screening of the patients was conducted in the form of taking medical history, physical examination and measuring vital signs (blood pressure, pulse rate, body temperature). In addition, analysis of liver enzymes and KOH mount for diagnosis were also conducted prior to treatment. Patients with abnormal laboratory results, or a history of hypersensitivity to azole compounds, or with any significant medical illness like diabetes or cardiac disease were excluded from the study.

Clinical study medications

Glenmark Pharmaceuticals Ltd, India, supplied all the drugs for the conduct of this study.

Clinical study design

This was a randomized, open-label, four-arm study, conducted to compare the rate and extent of serum and sebum concentration of SBITZ and CITZ at different dosing and to assess their efficacy and safety in patients with dermatophytosis. Eligible patients were randomized by computer-generated randomization into four groups to receive CITZ 100 mg BD, CITZ 200 mg OD (2 capsules of 100 mg), SBITZ 130 mg OD and SBITZ 100 mg OD (2 capsules of SBITZ 50 mg) for 4 weeks. During the entire study period, patients did not receive any other antifungal medications but were allowed to use a paraffin-based topical emollient. Analysis of liver enzymes and KOH mount were repeated at the end of therapy. The study design is shown in Figure 1.

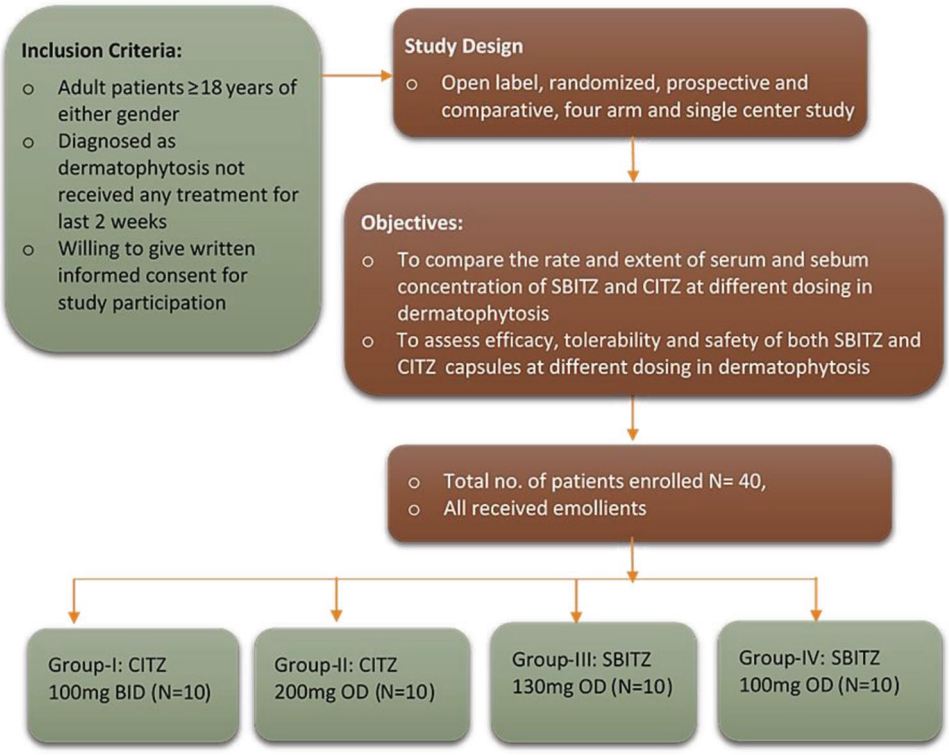
Plasma pharmacokinetics

A blood sample (~5 mL) was collected from every patient for plasma pharmacokinetic analysis at 0 hours (before dosing) and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after dosing. Additionally, blood was also collected on days 3, 7, 14 and 28. All blood samples on first day were collected by an IV catheter inserted into a forearm vein, whereas blood samples on days 3, 7, 14 and 28 were collected by direct venepuncture. All samples were collected in heparinized tubes and centrifuged at 4000 rpm for 15 minutes. Thereafter, plasma was transferred into polypropylene tubes and frozen at -20°C until further use. Only the parent analyte was measured in the plasma.

High-performance liquid chromatography analysis

The reported method[12] was modified and validated as per the FDA guidelines for the determination of ITZ in

Figure 1. Study design.



human plasma.[13] The concentration of ITZ in plasma was determined using high-performance liquid chromatography (HPLC; LC-10 AT VP, Shimadzu Corp., Kyoto, Japan) coupled with a UV-Vis detector (SPD-10A VP, Shimadzu Corp., Kyoto, Japan). The mobile phase consisted of acetonitrile and 0.05% diethylamine in the ratio of 60:40 (v/v). Chromatographic separation was performed using a C18 column (Phenomenex C-18, 4.6 × 250 mm, 5 µm) at flow rate of 1 mL/min with a detection wavelength of 258 nm. An aliquot of 1.0 mL from each plasma sample or sebum sample was mixed with 2.0 mL of acetonitrile followed by vortex mixing, for 5 minutes. The mixture was then subjected to centrifugation at 10,000 rpm for 10 minutes. The organic layer was separated, dried under a gentle stream of nitrogen and reconstituted with 200 µL of the mobile phase. Finally, 100 µL of the reconstituted sample were injected onto the HPLC column. The limit of quantification of the developed HPLC method was 2.0 ng/mL for ITZ.

Sebum concentration

It is well reported that ITZ gets accumulated in sebum and skin but not before 3 days post dosing.[5] Thus, sebum concentration for all strengths was determined on days 7, 14 and 28. The sebum of all patients was collected from the centre of the forehead according to the previously reported paper absorption method.[14] The area measuring 1.0 square inch was defined on the forehead and previously weighed rolling flax paper (OCB, France) was held over the demarcated area for 3 hours. At the termination of the test, the paper was weighed again to determine the quantity of sebum. Thereafter, papers were subsequently washed with three aliquots (1.0 mL) of acetonitrile to extract the ITZ. The samples were frozen at -20°C until further analysis.

Efficacy assessment

Efficacy assessment was considered as the number of patients achieving complete cure at the end of therapy. Complete cure was defined as achieving both clinical cure (complete lesion and symptom clearance) and mycological cure (KOH negative) in each group.

Safety

All patients receiving at least one dose of CITZ or SBITZ were evaluated for frequency as well as severity of adverse events (AEs) to determine the safety. Because ITZ is considered as hepatotoxic, liver function tests (SGPT, SGOT) were also performed to see any adverse effects of ITZ on the liver.

Statistical analysis

Pharmacokinetics parameters (C_{trough}) were calculated using WinNonlin version 7.0 (Certara Corporation,

Princeton, NJ, USA). Pharmacokinetic results were presented as mean scores, and groups were compared using one-way ANOVA with Tukey HSD test, whereas efficacy and safety were analysed by Fisher exact test. The level of significance was set at 0.05. Data were analysed using the IBM SPSS (Statistical Package for Social Sciences) statistics version 20.

Ethical considerations

The study was approved by the Independent Ethics Committee of Good Society for Ethical Research, Delhi, India and registered on CTRI (CTRI/2022/04/042183). The study was conducted per approved protocol by the ethics committee, recommendations under Schedule Y laid down by Central Drugs Standard Control Organization, Indian Council of Medical Research, Declaration of Helsinki (Brazil, October 2013) and Good Clinical Practices E6-R2, that is, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Informed consent forms were collected from all patients before the study.

Results

Study participants

Demographic information for all patients is summarized in Table 1. All samples from patients were considered for pharmacokinetics and clinical analysis.

Serum pharmacokinetics

Arithmetic mean ITZ plasma concentrations for all treatments increased steadily on day 1 through week 4 (Figures 2 and 3). We divided these serum pharmacokinetic results into three parts: (a) bioequivalence of SB formulations against CITZ 200 mg OD; (b) non-linear pharmacokinetics of ITZ; and (c) comparative analysis of both SB formulations.

Bioequivalence of SB formulations against CITZ 200 mg OD

On day 1, SBITZ 130 mg OD was found to be at bioequivalence with CITZ 200 mg OD (96%; range 80–125%) whereas SB 100 mg OD was found to be at 75% bioequivalence with CITZ 200 mg OD. From day 3 onwards, SBITZ and CITZ concentrations increased gradually until day 28. On day 28, both formulations of SB (SB 130 mg OD (103%) and SB 100 mg OD (89%)) were found to be bioequivalent to CITZ 200 mg OD.

Non-linear pharmacokinetics of ITZ

On day 1, the arithmetic mean and SD for CITZ 100 mg BD, CITZ 200 mg OD, SB 130 mg OD and SB 100 mg OD were 996±215.8 ng/mL, 1541±237.5 ng/mL, 1485±255.2 ng/mL and 1160±236.6 ng/mL, respectively. CITZ 200 mg OD, SBITZ 130 mg OD and 100 mg OD were found to have 1.55, 1.49 and 1.16 times higher serum concentrations than CITZ 100 mg BD. On day 28, CITZ 200 mg OD, SBITZ 130 mg OD and SB 100 mg OD were found to have serum concentrations 1.35, 1.40 and 1.2 times higher than that of CITZ 100 mg BD. On day 28, the arithmetic mean and SD for CITZ 100 mg BD, CITZ 200 mg OD, SB 130 mg OD and SB 100 mg OD were 1262±233.5 ng/mL, 1704±261.6 ng/mL, 1770±268.9 ng/mL and 1520±231.7 ng/mL, respectively, which was statistically significant for OD dosing of ITZ over BD dosing (Table 2). On intergroup comparison of serum concentration of OD dosing of ITZ, it was found that SB 130 mg OD was statistically significant compared with SB 100 ($p<0.05$) but no statistical difference was noted between SB 130 mg OD and CITZ 200 mg OD nor between SB 100 mg OD and CITZ 200 mg OD.

Comparative analysis of SB 130 mg OD and SB 100 mg OD formulations

SB 130 mg OD was found to have 1.28 times higher serum concentrations than SBITZ 100 mg OD on day 1. Although from day 3 onwards, concentration increased gradually until day 28 for both strengths but, on day 28, SBITZ 130 mg OD was found to have a serum concentration 1.16 times higher than that of SBITZ 100 mg OD. Arithmetic mean (SD) was statistically significant on day 1 ($p=0.008$) and day 28 ($p<0.05$).

Sebum concentration

Sebum concentration for SB 130 mg OD was better than for other strengths on days 7 and 14, and this trend

Table 1. Baseline demographics.

Parameters	CITZ 100 mg BD	CITZ 200 mg OD	SBITZ 130 mg OD	SBITZ 100 mg OD
N	10	10	10	10
Mean ± SD age (years)	35.2±4.5	34.7±4.8	34.6±5.1	34.3±5.2
Mean ± SD BMI (kg/m^2)	22.6	22.2	22.5	22.7
Mean ± SD weight (kg)	64.7±7.6	63.1±7.8	65.1±7.4	64.9±7.5
Mean ± SD height (cm)	169.2±5.1	168.6±5.4	170.2±4.9	169.2±4.8

BD, twice-daily; OD, once-daily.

Figure 2. Mean serum concentration of all ITZ on day 1.

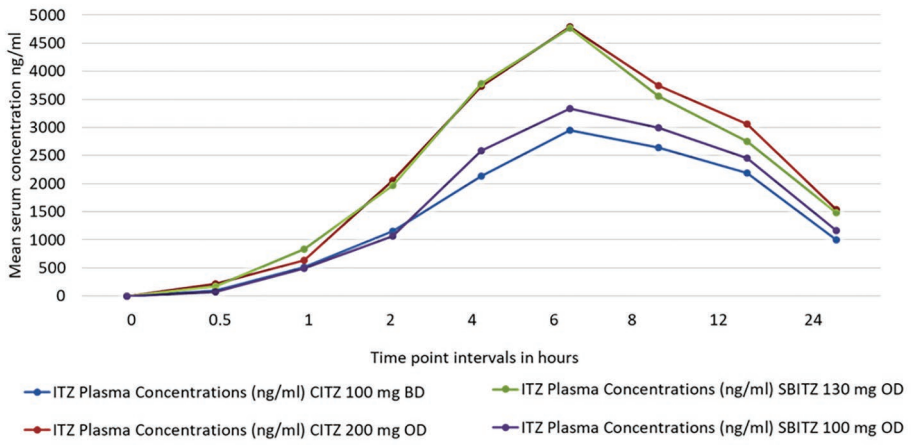


Figure 3. Mean serum and sebum concentration on days 7 and 14.

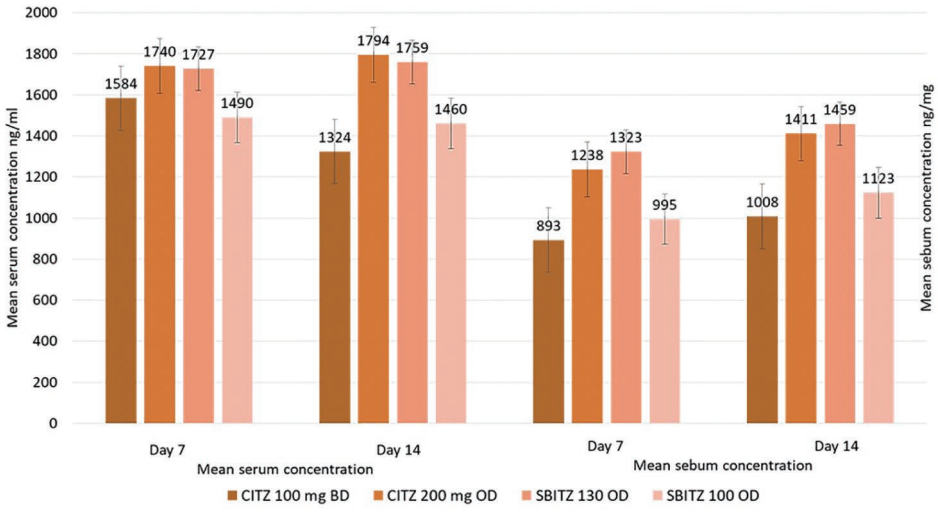


Table 2. Mean serum and sebum concentration for all itraconazole formulations and dosing on day 28.

ITZ dosing and formulations	Serum concentration			Sebum concentration		
	Mean ± SD	95% CI	*p* value	Mean ± SD	95% CI	*p* value
CITZ 100 BD	1262±233.5	1117.28–1406.72	0.05*	1052±163.45	950.7–1153.3	0.48[a]
CITZ 200 OD	1704±261.6	1541.86–1866.14		1423±192.46	1303.71–1542.30	
SBITZ 130 OD	1770±268.9	1603.34–1936.66		1534±227.55	1392.97–1675.03	0.05[b]
SBITZ 100 OD	1520±231.7	1376.40–1663.60		1107±182.35	993.98–1220.02	

*All OD formulations are statistically significant in relation to CITZ 100 BD; [a]SB 100 OD and CITZ 100 BD are not statistically significant; [b]SB 130 OD and CITZ 200 OD are statistically significant in relation to SB 100 OD and CITZ 100 BD.
BD, twice-daily; OD, once-daily.

continued until day 28 (Figure 3). On day 28, the arithmetic mean and SD for CITZ 100 mg BD, CITZ 200 mg OD, SB 130 mg OD and SB 100 mg OD were 1042±163.45 ng/mg, 1423±192.46 ng/mg, 1534±227.55 ng/mg and 1107±182.35 ng/mg, respectively, which was statistically significant for SB 130 mg OD and CITZ 200 mg OD over CITZ 100 mg BD and SBITZ 100 mg OD dosing (Table 2). There was no statistically significant difference between SB 130 mg OD and CITZ 200 mg OD (p=0.25). However, SB 130 mg OD had 1.45, 1.07 and 1.38 times higher sebum concentration than CITZ 100 mg BD, CITZ 200 mg OD and SBITZ 100 mg OD, respectively, on day 28.

Compared to day 14, a 3.2%, 0.8% and 4.9% increase was noted in mean sebum concentration in CITZ 100 mg BD, CITZ 200 mg OD and SBITZ 130 mg OD, respectively, on day 28; however, in the SB 100 mg OD group, there was 1.4% decrease in mean sebum concentrations. This was also noted for serum concentrations in the SB 100 mg OD group on day 28 compared with day 14.

Efficacy outcome

As shown in Table 3, two patients achieved complete cure in the SB 130 mg OD group whereas no patients in any other groups achieved the same. This difference was not statistically significant (p=0.47).

Safety outcomes

The administration of ITZ and SBITZ was generally well tolerated by all patients. A total of 12 treatment-emergent adverse events (TEAEs) were reported in ten patients (two each in the CITZ 100 mg BD and SBITZ 130 mg OD groups and three each in the CITZ 200 mg BD and SBITZ 100 mg OD groups) (Table 4). No patient discontinued treatment due to any TEAE. All TEAEs were mild in severity and resolved spontaneously. Additionally, no deterioration of liver enzymes was noted in any of the groups.

Discussion

Due to precipitous surge in incidence of dermatophytosis, many dermatologists are practicing different dosing patterns of ITZ, for example, 100 mg BD or 200 mg OD, and for longer durations. However, ITZ is a weak base lipophilic molecule with a limited 55% absolute bioavailability and, for better absorption, it must be administered with a full meal or cola beverages. Apart from this, it also possesses many other pharmacokinetic challenges such as inter-individual and intra-individual variability, reduced absorption in the presence of proton pump inhibitors, and so on. To address these challenges, an oral solution of CITZ was developed and approved in 1997.[15] However,

Table 3. Cure rates for CITZ and SBITZ.

Efficacy parameters	CITZ 100 mg BD	CITZ 200 mg OD	SBITZ 130 OD	SBITZ 100 OD	*p* value
Complete cure	0	0	2	0	0.47[a]
Mycological cure	1	2	3	3	
Clinical cure	0	0	2	0	

[a]Not statistically significant.
BD, twice-daily; OD, once-daily.

Table 4. Treatment-emergent adverse events in all groups.

	No. (%) of patients with treatment-emergent adverse events			
System organ class term	CITZ 100 BD (n=3)	CITZ 200 OD (n=3)	SBITZ 130 OD (n=3)	SBITZ 130 OD (n=3)
Gastrointestinal disorders				
Abdominal pain	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Diarrhoea			2 (20%)	1 (10%)
Nausea	2 (20%)	1 (10%)		
Nervous system disorders				
Headache		1 (10%)		1 (10%)

BD, twice-daily; OD, once-daily.

this solution was found to be unpalatable and increase the absolute bioavailability only up to 72%. Although CITZ has broad-spectrum activity,[16,17] the difficulty in attaining the therapeutic plasma levels owing to pharmacokinetic challenges has limited its use. Indeed, ITZ was detected only in about 60% of the blood samples tested.[9] Therefore, SBITZ was developed to overcome these pharmacokinetic challenges, providing a more persistent plasma concentration, minimally altered by gastric acid-suppressive agents and exhibiting comparable absorption under both fasting and fed conditions. Hence, SBITZ provides improved drug delivery compared with CITZ.

In India, ITZ is approved in invasive mycosis by the DCGI.[18] Because SBITZ is an improved formulation of CITZ, indications approved for CITZ are also applicable for SBITZ. However, in India, ITZ is commonly prescribed in the management of dermatophytosis and therefore so is SBITZ. Recently, many strengths of SBITZ were approved by DCGI,[10,11] creating dilemma at the dermatologist's level regarding prescription of SBITZ in dermatophytosis. Hence, the present study was outlined to compare the rate and extent of serum and sebum concentrations of SBITZ and CITZ at different dosing and to determine their efficacy and safety in patients with dermatophytosis.

Due to its non-linear pharmacokinetic profile, ITZ is commonly prescribed OD. However, in India, it is commonly prescribed as BD. Herein, it was found that serum concentration of SB 130 mg OD, CITZ 200 mg OD and SB 100 mg OD were much higher than CITZ 100 mg BD. This indicates that, to achieve better serum concentrations, ITZ should be prescribed as OD dosing. On day 1 only, serum concentrations of SB 130 mg OD were found to be 1.5 times higher than CITZ 100 mg BD. Similar findings were also noted for SB 100 mg OD and CITZ 200 mg OD. This trend of higher serum concentrations continued until day 28, with SB 130 mg OD having 1.4 times higher serum concentration than the CITZ 100 mg BD.

ITZ has complex and highly variable pharmacokinetics, especially after oral administration. It follows non-linear pharmacokinetics in a comparison of single *versus* multiple-dose administration.[19,20] Because of non-linearity in pharmacokinetics, there is a disproportionate increase in ITZ plasma concentration. Heykants et al.[19] and Hardin et al.[20] have concluded that oral absorption and bioavailability of ITZ are a function of dose. Non-linear increase in the AUC and C_{max} were reported after oral doses of 50, 100 and 200 mg, pointing out a saturation of the first-pass metabolism process in the liver.

Recently, in India, many strengths of SBITZ were approved by the CDSCO, creating dilemma at the physician level. The result of this study demonstrated that SB 130 mg OD achieved 1.28 times higher serum concentrations than SB 100 mg OD on day 1 only, which increased until day 28 where it was 1.16 times higher than SB 100 mg OD. Some previous studies have found that C_{trough} ITZ levels should be between 1000 and 2000 ng/mL for treatment and >500 ng/mL for prophylaxis against deep mycosis.[21–26] However, Khurana et al. indicated a cut-off value of serum concentration of 200 ng/mL in dermatophytosis.[27] Although toxicity levels of plasma ITZ are challenging to assess, some studies indicated that C_{trough} levels between 2,000 and 5000 ng/mL are suggestive of increased side-effect profiles.[28,29] In present study, C_{trough} levels from day 1 onwards were never above 2000 ng/mL in any of the groups, indicating safety even at high OD dosing.

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.[6] The concentration of ITZ in sebum is crucial as its distribution in the skin, especially stratum corneum, is extensively dependent on sebum production.[30] In usual kinetic studies, only serum kinetics and drug susceptibility are evaluated and the kinetics at the target site, that is, skin (in case of dermatophytosis) are not considered, which is why susceptibility parameters of systemic antifungals do not consistently correlate with in vivo efficacy in the treatment of dermatophytosis. Such sebum evaluation studies of oral antifungals are very scarce.[5,6]

In the present study, sebum concentrations of SBITZ 130 mg OD were 1.45, 1.07 and 1.38 times higher than for CITZ 100 mg BD, CITZ 200 mg OD and SBITZ 100 mg OD, respectively, at the end of the study, and this difference was statistically significant ($p<0.05$) compared to CITZ 100 mg BD and SB 100 mg OD but no significant difference was noted against CITZ 200 mg OD ($p=0.25$). However, no statistical difference was found between SB 130 mg OD and CITZ 200 mg OD. Nevertheless, in our study, we used two capsules of ITZ 100 mg and not the single capsule of ITZ 200 mg. Sardana et al.[31] mentioned the limitation of ITZ 200 mg capsule and raised the question on the quality of CITZ 200 mg as a single capsule in manufacturing process.

In our study, sebum concentrations were found to be slightly less than the corresponding serum concentration, which is not in accordance with previous studies where sebum concentrations were found to be 2–5 times higher than serum concentrations.[5] This could be due to differences in the methods of assessment of sebum concentration, where Cauwenbergh et al.[5] measured sebum concentrations directly from sebaceous gland whilst, in our study, it was measured by paper absorption method. A previous study[32] observed a slow

transfer of ITZ from lower epidermis to upper epidermis due to high binding to epidermal proteins. Sobue et al.[33] also concluded strong binding of ITZ to corneous keratin.

Nevertheless, sebum concentrations of all formulations were found to be above the minimum inhibitory concentration (MIC) levels of ITZ. Shaw et al.[34] demonstrated MICs of ITZ against *Trichophyton mentagrophytes* in the ranges 7.8–1000 ng/mL. Because the mean sebum concentration of all formulations was above 1000 ng/mg, all formulations were supposed to be effective in dermatophytosis; however, in our study, only two patients in the SB 130 group achieved complete cure as compared to none in other groups. 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 cure in all groups; however, this difference was not statistically significant.

There were only 12 TEAEs reported from ten patients and were mild in intensity. This was not in line with other studies where relatively higher TEAEs were reported.[2,35–37] ITZ is known to cause some mild gastrointestinal complaints like nausea or abdominal pain, headache, and elevation of transaminase levels, which lead to treatment discontinuation. However, in present study, there was no elevation of transaminase levels nor discontinuation of treatment.

Conclusion

From this study, it was concluded that all formulations achieved desired serum and sebum concentration required for efficacy in dermatophytosis. However, OD formulations of ITZ were found to be statistically significant in relation to CITZ 100 mg BD in terms of achieving serum concentration due to non-linear pharmacokinetics and SB 130 mg OD and CITZ 200 mg OD were statistically significant in relation to SB 100 mg OD in achieving sebum concentration. Therefore, it can be concluded that SBITZ 130 mg OD was bioequivalent to CITZ 200 mg OD and achieved similar results to those of CITZ 200 mg OD but at 35% lower drug concentrations.

Limitations

It must be noted that only sebum concentrations were evaluated and we could not evaluate stratum corneum concentrations and MIC of the isolates. Furthermore, the small sample size and short duration of therapy were other limitations of this study, yet the results provided useful information regarding different formulations of ITZ. However, a comparative clinical study with SBITZ 130 mg OD and CITZ at different dosing in the management of dermatophytosis (CTRI/2021/11/038275, PI; Bela Shah) is under way to evaluate the efficacy and safety of the formulations and the different strengths.[38]

Contributions: DD, GJ and NM have made substantial contributions to conception and design. GJ, MM and PK contributed to the literature search, clinical study and data acquisition. Data analysis and manuscript writing were performed by DD and NM, whilst HB was involved in manuscript editing. DD and NM were involved in drafting the manuscript or revising it critically for important intellectual content. All authors had given final approval of the version to be published. Each author had participated sufficiently in the work to take public responsibility for appropriate portions of the content. DD and NM agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: NM, DD and HB are working with Glenmark Pharmaceuticals Ltd, India. The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2022/12/dic.2022-8-1-COI.pdf

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