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Review Article

Efficacy of super bioavailable itraconazole in the management of dermatophytosis in India

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ABSTRACT

Itraconazole (ITZ) is a commonly prescribed oral antifungal agent in India and has a low minimum inhibitory concentration when compared to other oral antifungals. However, clinicians have reported inconsistent clinical responses despite its high skin levels, which may be due to variations in pelletization parameters, which affect its bioavailability and serum levels. Conventional ITZ has a maximum bioavailability of 55%; however, this is unpredictable and inconsistent. In contrast, the novel ITZ formulation, super bioavailable ITZ (ITZ-SB), has targeted drug release in the small intestine, resulting in predictable serum levels with minimal interindividual variability. This makes it a potentially useful drug in treating recalcitrant dermatophytosis. This expert opinion highlights the benefits of novel ITZ-SB with the incorporation of SUBA® technology. The SUBA® technology improves the bioavailability of poorly soluble drugs by 'solid dispersion' in polymer to increase drug absorbency. This technology also has potential to reduce variability in absorption and adverse effects. Benefits of this technology include more predictable clinical response and lower drug quantities necessary to achieve therapeutic blood levels, making it a promising treatment option for recalcitrant dermatophytosis. Fixtral SB, which uses this technology, is a novel weapon in the arsenal of treatments for superficial mycoses.

Keywords: Mycoses, ITZ, Antifungal agents

INTRODUCTION

Dermatophytosis is an emerging global public health challenge, with the world health organization (WHO) reporting a worldwide prevalence of 19.7%.[1] In India, the incidence rate of dermatophytosis ranges from 36.6% to 78.4%, with a higher prevalence in hot and humid regions as compared to regions with moderate climate. Cases of chronic, recalcitrant, and recurrent dermatophytosis are increasing rapidly in India due to increased urbanization, poverty, overcrowding, and the host immunosuppression.[2,3]

The emergence of recalcitrant dermatophytosis, particularly in the form of Tinea corporis and T. cruris, the most prevalent fungal infections in humans, has become a global cause for concern in recent years, resulting in more studies into the management of this condition. A critical characteristic of the drugs used to treat superficial mycoses is their capacity to effortlessly permeate the stratum corneum and maintain a stable concentration throughout treatment.[2,4]

Super bioavailable ITZ (ITZ-SB) is the product of a novel technology that improves the bioavailability of poorly soluble agents by enhancing their dissolution.[5]

The uniform structure of this formulation features a pH-dependent hypromellose phthalate (HPMCP) polymeric matrix, which releases the drug in the small intestine and is more soluble than conventional itraconazole (ITZ-C). With high bioavailability and minimal interindividual response variability, ITZ-SB is an effective treatment option for dermatophytosis.[6] There is evidence that ITZ-SB has better remission rates than ITZ-C as ITZ-SB allows a high concentration of the drug to accumulate at the target site. This is the most important predictor of antifungal therapy outcomes and results in extensive eradication of fungi from the lesions, with a higher mycological cure rate as evidenced in patients receiving ITZ-SB for the treatment of onychomycosis.[7] Globally, ITZ-SB is currently approved in two strengths: 50 mg (approved in Europe and Australia) and 65 mg (approved by the US FDA).[7-10] In India, there are currently four doses of ITZ-SB approved by the drug controller general of India (DCGI)/Central drugs standard control organization (CDSCO): 50 mg, 65 mg, 100 mg, and 130 mg recommendations of the SEC [Dermatology and allergy] made in its 46th meeting; Recommendations of the SEC [Antimicrobial and antiviral] made in its 102nd meeting; recommendations of the SEC [Dermatology and allergy] made in its 61st meeting; recommendations of the SEC [Antimicrobial and antiviral] made in its 103rd meeting).[11]

An expert panel comprising of renowned panelists with over 25 years of experience in clinical and cosmetic dermatology and aesthetics was selected for the advisory board meeting (ABM). All panelists had more than ten publications in reputed peer-reviewed journals.

This expert opinion aimed to highlight the prevalence of dermatophytoses in Indian population, and the efficacy of ITZ-SB in the management of clinical symptoms. It also highlights the benefits of an ITZ-SB formulation, Fixtral SB, as compared to ITZ-C formulation.

PHARMACOKINETICS OF ITZ

ITZ, a triazole antifungal with a broad-spectrum activity, was approved for use by the Food and Drug Administration (FDA) in the United States in the 1990s. It is a weakly basic drug with a pH-dependent (pKa=3.7) dissolution rate and requires an acidic gastric environment for dissolution and absorption.[12,13] It has a bioavailability of 55%, which is influenced by food intake; however, several drawbacks are associated with the use of ITZ-C.[12,14]

Expert opinion on ITZ-C pharmacodynamics

As per expert opinions, the parent drug, ITZ-C, has poor pH-dependent solubility in the intestinal environment with only a 12% release. As ITZ-C has a pH-independent polymer, 75% of it dissolves in the stomach environment, and after gastric emptying, it precipitates at intestinal pH (>5.0). Second, ITZ-C has extremely low aqueous solubility, poor dissolution rate, erratic absorption, and inconsistent drug concentrations. Third, due to poor solubility and inconsistent drug concentration, ITZ-C has only 55% bioavailability. For instance, 200 mg Sporanox® (ITZ-C), mathematically, will give 100 mg of the bioavailable drug. Based on these challenges, there was a need for a better ITZ formulation that addressed the need of achieving better patient compliance and enhanced absorption and bioavailability and demonstrated consistent drug concentrations, good dissolution rate, and less inter-/intrasubject variability in response.

ITZ-SB VERSUS ITZ-C

For a drug to be optimally effective, absorption and bioavailability should have minimal variability between individuals. However, the interindividual variability of ITZ-C can be as high as 50-60% with a bioavailability of 50%–55%, which is also inconsistent. The absorption of ITZ-C is unpredictable due to its pellet formulation, as the drug release from the polymer is dependent on the gastric environment. This dependence results in erratic absorption and subtherapeutic drug concentrations in the blood and causes treatment failure, drug toxicity, or drug resistance.[4]

Expert opinion on the factors affecting the therapeutic effect of ITZ-C

The experts opined that the factors that inhibit ITZ-C's therapeutic effect are as follows: Use of proton pump inhibitors (PPIs) with ITZ therapy, which increases stomach pH, resulting in precipitation of ITZ-C in the stomach, hence decreasing its absorption. Substandard formulation of ITZ. Needs to be taken after full-fat meal, which may lead to noncompliance in certain patients

ADVANCED POLYMERIC SPRAY GRANULATION (APSGTM) TECHNOLOGY: AN ADVANCED ANTIFUNGAL DELIVERY SYSTEM

The introduction of pelletization has enhanced the bioavailability of ITZ formulations, resulting in superior therapeutic effects over conventional single-unit drug delivery systems. The pellets disperse uniformly throughout the gastrointestinal tract, thus minimizing the risk of drug toxicity. Pelletization also reduces interpatient variability in absorption by reducing the variations in gastric emptying rates and transit times.[4]

Expert opinion on APSG™ technology

According to the experts, Fixtral SB comes with an advanced polymeric spray granulation (APSG™) technology that uses a novel polymer-drug solution (HPMCP) and an inert carrier to generate an amorphous solid dispersion. This ternary mixture of drug-polymeric solution is spray-dried onto a highly water-soluble inert carrier drug–polymer, which exhibits superior solubility, absorption, and stability (Figure 1).

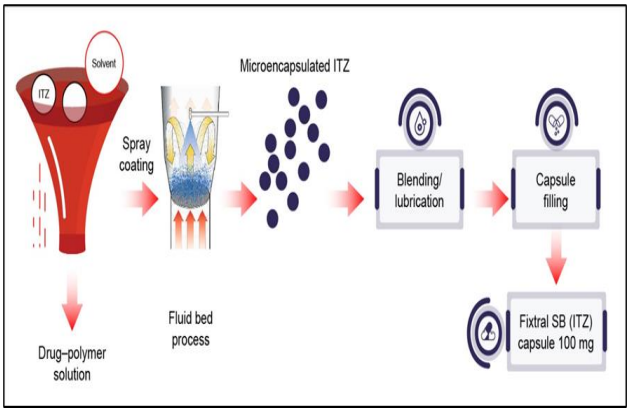

Figure 1: APSG™ technology explained.[12]
ITZ: Itraconazole; SB ITZ: Super bioavailable itraconazole.

Furthermore, the experts stated that: The selected polymer confers a total release of contents in the intestine creating a microenvironment with a resultant ≥98% release of ITZ at an intestinal pH (>5.0) for the maximum intestinal absorption, whereas interestingly, only 2% gets released in the stomach. The spray-coating process produces uniform microencapsulated particles of ITZ in an HPC-phthalate solid dispersion. This process is robust and reproducible and optimized by X-ray diffraction studies; the drug-polymer ratio is optimized to retain its amorphous form throughout its ITZ-SB shelf life, thus increasing absorption and bioavailability by 30%, which is higher than that of ITZ-C. Previously, SUBA® technology used the HPMCP polymer to enhance oral bioavailability and to address the problems of poor solubility and precipitation of ITZ-C at intestinal pH (>5.0). It was reported that 50 mg of SUBA® technology-driven ITZ is therapeutically equivalent to the minimum inhibitory concentration (MIC) levels of 100 mg of ITZ-C. To overcome the current limitations of ITZ-C, Dr. Reddy's® ITZ-SB was developed, with therapeutic equivalence to Sporanox® 200 mg. Its superior quality is due to design principles inclusive of the grade of polymer, drug-polymer ratio, and several other preformulated and process parameters to arrive at control strategies for consistent product performance.

BIOEQUIVALENCE DATA

Therapeutic equivalence calculated by the area under the curve of drug concentrations vs. time/minimum inhibitory concentration (AUC/MIC) ratio is widely used for regulatory acceptability of the antifungal class of drugs. The results of a bioequivalence study that compared Fixtral SB to an ITZ-C formulation (Lozanoc®) are shown in Table 1.

The study reported that ITZ-SB (100 mg) was equivalent to Lozanoc® (50 mg) capsule bis in die (BD), as determined by the AUC/MIC ratio; the test product (Fixtral® SB or ITZ-SB; 100 mg) was also found to be therapeutically equivalent to the reference product (Sporanox® capsules; 100 mg) for each MIC level (Table 2 and Figure 2). Hence, based on these data, the DCGI has approved the use of ITZ-SB (100 mg).[12]

Table 1: Bioequivalence comparison of Fixtral SB (100 mg) with Lozanoc® (100 mg).[12]

Variables	Geometric mean		Ratio (T/R) (%)	90% CI limits (%)		Power (%)	Bioequivalence
	Fixtral SB	Lozanoc®		Lower	Upper		
C_{max}	117.4	118.82	98.81	88.57	110.22	91.79	Yes
AUC0-t (ngxh/mL)	2533.47	2794.45	90.66	83.31	98.65	99.02	Yes
AUC0-nf (ngxh/mL)	2856.78	3212.68	88.92	81.57	96.92	98.79	Yes
Kel	0.022 (0.007)	0.021 (0.007)					
T1/2 (minute)	34.89 (13.18)	37.83 (14.95)					

Acceptance criteria for primary parameters: 80-125.00%. AUC0–t: Area under the concentration–time curve over the dosing interval; AUC0-inf: Area under the curve; C_{max}: Maximum concentration; Kel: Elimination constant; t1/2: Time required for plasma concentration of a drug to decrease by 50%; T/R ratio: Test/reference ratio.

Table 2: Mean therapeutic parameters of Fixtral SB (100 mg) as compared with those of Sporanox® (100 mg) and Lozanoc® (100 mg).[12]

Variables	Mean ± SD		
	Fixtral SB	Sporanox®	Lozanoc®
C_{max}	132.12 (65.31)	308.57 (173.63)	136.90 (67.91)
AUC0-t (ngxh/mL)	2738.083 (1164.121)	4953.205 (2472.121)	3065.766 (1295.989)
AUC0-inf (ngxh/mL)	3109.578 (1342.394)	5744.760 (2917.508)	3614.170 (1850.356)
T_{max} (min)	11.45(6.05)	6.00 (1.49)	10.85 (6.33)
Kel	0.022 (0.007)	0.021 (0.007)	0.023 (0.008)
T1/2 (min)	34.89 (13.18)	37.83 (14.95)	35.16 (20.14)

AUC0-t: Area under the concentration-time curve over the dosing interval; AUC0–inf: Area under the curve; C_{max}: Maximum concentration; Kel: Elimination constant; SD: Standard deviation; T_{max}: Time required for peak drug concentration; t1/2: Time required for plasma concentration of a drug to decrease by 50%.

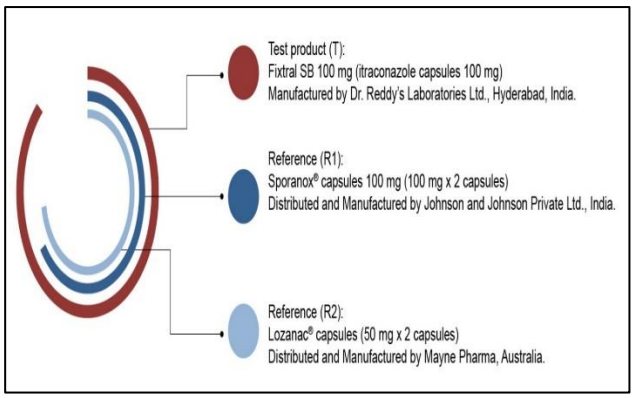

Figure 2: Bioequivalence study design.[12]

Expert opinion on commercially available ITZ-SB

As stated by experts, Mayne Pharma initially launched Lozanoc® 100 mg and 50 mg, based on SUBA® technology in the US and other countries. For therapeutic equivalence, an MIC between 4 and 16 µg/mL and an AUC/MIC ratio >25 are acceptable, which were demonstrated by both doses. The European and Australian regulatory bodies approved 100 mg strength for Lozanoc®. US-FDA authority considers bioequivalence and bioavailability study outcomes, and Mayne Pharma faced obstacles in getting approval to prove classical bioequivalence with 200 mg of Sporanox®. As per US-FDA norms, Lozanoc® 100 mg once daily (OD) bioequivalence was found to be 70-75% acceptability limits of Sporanox® 100 mg BD, albeit it should be between 80% and 125% acceptability limits.

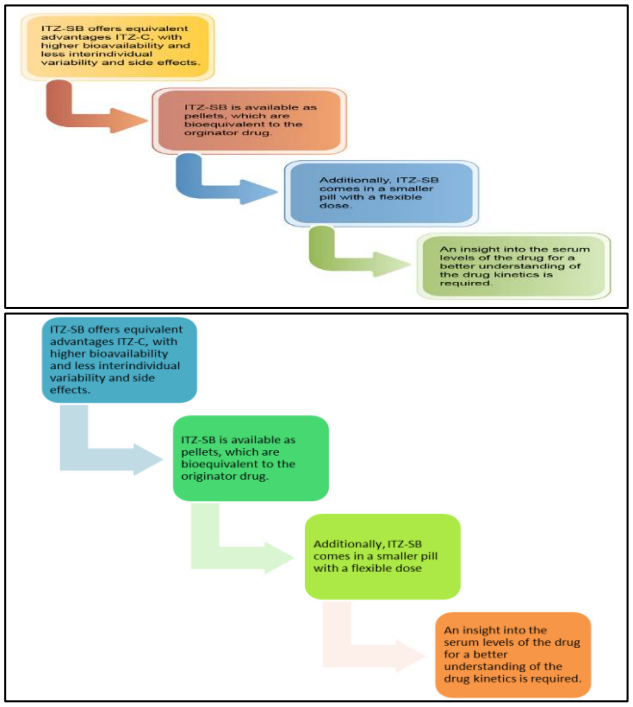

Figure 3: Advantages of Fixtral SB.
ITZ-C: Conventional itraconazole; ITZ-SB: Super bioavailable itraconazole.

COMMON SUPERFICIAL AND DERMATOLOGICAL FUNGAL INFECTIONS ENCOUNTERED IN DAILY PRACTICE

An 80-year retrospective epidemiological analysis of dermatophytosis in India discusses the prevalence of this condition over time and across the country, concerning the temporal variations in climate. The study found that T. rubrum was the most common causative agent until 2015, but there has been a recent shift toward T. mentagrophytes/T. interdigitale complexes.[15]

Another systematic review that compared the antifungal susceptibility to terbinafine among Trichophyton species worldwide found that around 30% of the studies were carried out in the India, highlighting the significant burden of the emerging drug resistance epidemic in the country.[16]

Expert opinion on the prevalence of dermatophytosis in India

In recent years, India has experienced an epidemic of dermatophytosis despite regional variations in the climate, with several contributing factors leading to the increase in fungal infections, a decline in quality of life, and increased morbidity. The causative agents have also become more resilient to temperature changes, with Mentagrophytes being increasingly common.

As per the expert opinions, the prevalence of dermatophytosis was relatively higher in the coastal parts of the country, thereby considering the tropical climate of the country as a predominant factor for the increase in dermatophytosis.

The experts opined that the disease remission rate was found to be higher in South India when compared to that in North India.

In rural areas of the northern part of India, access to dermatologists is limited as compared to southern regions, and topical steroid misuse is also more prevalent; therefore, there is a lower resolution rate of dermatological fungal infections in these areas.[17]

CONSENSUS GUIDELINE OR RECOMMENDATION FOR THE DURATION OF TREATMENT

In India, certain predisposing factors contribute to the misuse of antifungal medications, such as over-the-counter (OTC) availability and rampant use of topical steroids and antifungal combinations by patients. Despite the lack of consensus guidelines, dermatologists are using a combination of higher doses, and longer treatment durations of oral antifungals and retinoids to manage recalcitrant cases. However, this approach is more of a hit-and-trial method rather than the evidence-based practice.[2]

Expert opinion on treatment strategies for dermatophytosis

The experts have opined that textbook treatments may not be sufficient for practical use, as many patients often seek treatment for recalcitrant situations. It is desirable to optimize the frequency of visits and doses accordingly. The standard practice for the treatment of skin infection involves administering oral medication for 3 months, and following clinical resolution, the medication should be gradually tapered off.

TIMING OF CLINICAL INVESTIGATIONS

Antifungal susceptibility tests are far more complex than antibacterial tests and are best performed by reference laboratories. Standard guidelines framed by the clinical laboratory standards institute (USA) and European committee on antibiotic susceptibility testing recommend the broth microdilution method as the standard test for dermatophytes. The lowest concentration of antifungal agent that can inhibit growth is determined by the MIC; however, it does not always correlate with clinical responses.[18]

Expert opinion on the need for new pharmacological agents to treat dermatophytosis

The experts opined that there is a need to discover new pharmacological agents and conduct more clinical trials to determine their efficacy and safety in managing dermatophytosis. Studies on different formulations of ITZ to frame uniform guidelines or arrive at a consensus based on clinical experience are desirable. There is a need for a scoring system for the number of lesions of *Tinea* species to enable dermatologists to decide the treatment course and duration.

Expert opinion on the treatment protocols for ITZ-SB

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. 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. 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.

COUNSELING AND ADMINISTRATION OF ORAL ANTIFUNGAL AGENTS IN CLINICAL PRACTICE

Dermatologists possess a diverse array of antifungal medications at their disposal. Although the application of a topical antifungal agent typically proves effective in eradicating the dermatophyte, certain challenges, notably, colonization by T. capitis and T. unguium, frequently necessitate systemic therapy.[19]

The emergence of drug resistance is a major problem in India. Dermatologists recommend the use of combination therapies of topical antifungal drugs, higher dosages, and a longer duration of treatment with existing antifungal drugs and, occasionally, oral retinoids, to manage recalcitrant Tinea infections.[2,18]

Antifungal medications, such as griseofulvin or fluconazole, previously demonstrated favorable clinical outcomes; however, it is crucial to conduct baseline liver and renal function tests and consistent monitoring when considering the use of higher doses of these systemic antifungals, while also being mindful of drug interactions, particularly in patients taking multiple medications.[20] The MIC values for fluconazole, griseofulvin, and terbinafine are increasing; however, the MIC values for ITZ and ketoconazole are low for all species of dermatophytes, thus showing that these drugs may be a better option for effectively treating dermatophytic infections.[21]

Terbinafine in combination with ITZ is also commonly prescribed; however, emerging drug resistance patterns at low concentrations of this drug necessitate the use of higher concentrations. A recent randomized controlled trial compared the efficacy of terbinafine and ITZ for the treatment of T. corporis and T. cruris and concluded that terbinafine had a higher failure rate when compared to ITZ, which had superior clinical and mycological cure rates.[22] Most of the experts have observed the resolution of clinical symptoms in patients after prescribing ITZ-C (100 mg) monotherapy, fluconazole, or terbinafine. Most of the brands of ITZ-C were effective, except for a few brands that were found to be inferior in their action.

Experts considered ITZ as the first-line treatment for cutaneous dermatophytosis due to its low MIC value and lipophilic nature, which allows it to be easily absorbed into the skin and deposited on the keratin layer for effective therapeutic action. Currently, there are two strengths of ITZ-SB approved globally: 50 mg (approved in Europe and Australia since 2019) and 65 mg (approved by the US FDA since 2018)[7,8] FDA Approves SUBA-ITZ for Treatment of Systemic Fungal Infections; Center for Drug Evaluation and Research). The US FDA has

also approved a dose of 130 mg SB ITZ BD in the management of systemic mycosis (Pappas, 2020). In India, there are currently four dose approved by the DCGI/CDSCO: 50 mg, 65 mg, 100 mg, and 130 mg.[11] There is no evidence supporting a BD dose of ITZ, but clinically, practitioners prescribe a BD dose of ITZ.[14]

The consensus on the management of dermatophytosis in India, 2018, recommends topical monotherapy for naïve localized T. corporis, and a combination of topical and oral therapies for extensive T. corporis, recalcitrant T. corporis, and naïve or recalcitrant T. pedis.[23] In a survey conducted on 220 dermatologists, 87.3% of the dermatologists reported a rise in Tinea fungal infection cases in India, and the majority preferred a combination of oral and topical azoles as the treatment of choice for superficial dermatophytosis.[24]

Expert opinion on patient counselling

The experts opined that providing counselling in a hospital setting can be challenging and could be more feasible in private practice. Counselling, in conjunction with medication, is essential for the effective treatment of dermatophytosis. Most patients in private practice receive counselling from clinicians, along with informational materials outlining the dos and don'ts. Using visual aids could prove to be more beneficial in promoting preventive measures. Clinicians must determine the appropriate time to counsel the patient.

SKIN KINETICS OF ITZ

ITZ enters the skin through passive diffusion from the bloodstream and is also excreted from the sebaceous glands. Sweat excretion, which is the main delivery route for griseofulvin, appears to be a minor pathway for ITZ. According to the experts, although several antifungal therapies are currently available, more data on skin kinetics and drug studies are needed to assess their efficacy.[25]

Even in the absence of measurable plasma levels, the high affinity of ITZ for keratinous tissue and its persistence in this tissue make it a suitable treatment for superficial mycoses. Additionally, ITZ is not redistributed into the systemic circulation after being incorporated into the skin or nails, and persists even after therapy, depending on the site of the infection. Although clearance from the systemic circulation occurs within 8-10 days, a 1-week-long pulse therapy is generally required.[25]

A study comparing a 65 mg BD ITZ-SB course with a 50 mg BD ITZ-SB course found a statistically significant higher trough concentration of ITZ-SB with the 65 mg ITZ-SB course than with the 50 mg ITZ-SB course ($p<0.05$); there was also a higher sebum concentration of ITZ at 7 days and 14 days in the 65 mg ITZ-SB group ($p<0.05$).[26] Another randomized study compared the efficacies of ITZ-C (100 mg BD), ITZ-C (200 mg OD), ITZ-SB (130 mg OD), and ITZ-SB (100 mg OD) used for 4 weeks and reported that 130 mg ITZ-SB OD had 1.28 times greater serum concentration of ITZ than 100 mg ITZ-SB OD on day 1, which kept increasing till the 28th day. The ITZ concentrations in the sebum for ITZ-SB (130 mg OD) were 1.45, 1.38, and 1.07 times greater than those for ITZ-C (100 mg BD), ITZ-SB (100 mg OD), and ITZ-C (200 mg OD), respectively. The observed levels did not exceed 2000 ng/mL in any of the groups, thus demonstrating the safety of ITZ-SB even at higher OD doses.[27]

EFFECT OF THE BIOAVAILABILITY OF ANTIFUNGAL AGENTS ON TREATMENT FAILURES OF DERMATOPHYTOSIS

The American academy of family physicians recommends continuing topical antifungal treatment for at least 1 week after clinical resolution. However, experts suggest that treatment should continue for 2 weeks after clinical cure, which is consistent with a recent review of dermatophytosis in India.[18]

Expert opinion on treatment failure

As per experts, treatment failure occurs mainly due to nonadherence and noncompliance of patients to the prescribed treatment. In a few cases of reactivation or recalcitrant infection, 90% of cases are remitted based on counselling. The experts also preferred ITZ-SB as it can be given with or without food.

It has been noted that the cost of these medications can also be a factor in poor compliance. Topical antifungal creams can be expensive and may not last long, leading patients to choose less-expensive steroid-containing combinations that provide quick relief but worsen the disease over time. With the increasing problem of chronic/recurrent dermatophyte infections in India, many pharmaceutical companies have started manufacturing ITZ and terbinafine, but bioavailability studies for most of these formulations are lacking.[2]

DIFFERENT STRENGTHS OF ITZ FORMULATION AVAILABLE IN THE MARKET

The experts opined that ITZ-C 100 mg BD is the most widely accepted dose. Lozanoc® 50 mg (Mayne Pharma) was approved in European countries, which is equivalent to 100 mg ITZ-C (Sporanox®), and Fixtral SB was developed on a similar concept as Lozanoc® 50 mg; that is, ITZ-SB 100 mg OD is equivalent to Sporanox® 100 mg BD.

According to the available treatment guidelines for dermatophytosis in Europe and the United States, the dose recommendation for ITZ is 200 mg OD, whereas as per the Indian consensus guideline, the dosage is 100 mg BD.[23] For nonadherent patients, a dosage of 130 mg OD

is better; however, as per other experts, the dosage of ITZ-C (100 or 200 mg) must be BD for at least 2 weeks, because pharmacokinetically, it takes 2 weeks for ITZ to reach the steady state in the body.[14] Combination therapy appears to be effective, except for ~2% of cases where patient adherence, family contribution, and cost affected the treatment outcome.[2]

Expert opinion on the use of ITZ-SB in special populations

As per expert opinions, ITZ-C 100 mg BD is the most widely accepted dose, and the dose depends on the patient's weight, body surface area, and metabolism; the dose of ITZ-SB is 3 mg/kg body weight lower than that of ITZ-C. Experts agreed that ITZ-SB was a more suitable option than ITZ-C in the management of dermatophytosis: It can be taken with PPIs, interindividual variation in bioavailability is less, it is cost-effective, due to fewer doses required and it can be given in the presence or absence of food.

Experts opined that the advantage of ITZ-SB was its amorphous nature, which increased its absorption. Sensitivity assays performed for ITZ-C would yield similar results as ITZ-SB, and the exact MIC levels are not yet known for ITZ-SB. The experts opined against the prescription of ITZ (either ITZ-C or ITZ-SB) in patients with congestive heart failure (CHF).

A 10-year retrospective cohort study was conducted to analyze patients with ITZ and cardiac toxicity and reported that 74% of patients had edema, followed by heart failure; these symptoms resolved when ITZ was discontinued, concluding that ITZ can lead to serious cardiac adverse events.

ITZ is the contraindicated in patients taking calcium channel blockers (CCBs) due to its negative ionotropic effect on the heart as well as its cytochrome P450 3A4 (CYP3A4) inhibitor properties, which increase the CCB levels.[28]

Expert opinion on use of ITZ in medically compromised patients

The experts opined that although ITZ should not be administered in patients with CHF and on CCBs as per the contraindications, if ITZ-SB or another super bioavailable ITZ formulation was to be administered in such cases, it should be for a shorter duration, as prolonged exposure to multiple drugs can cause hepatotoxicity. The experts did not recommend the use of ITZ for patients with severe liver ailments, such as Gilbert's syndrome; however, intensivists may now prescribe ITZ to patients with benign Gilbert's syndrome under careful observation.

The exact relationship between ITZ and hepatotoxicity is unclear, but there may be a correlation between the drug's ability to affect sterol synthesis and its inhibitory effect on P450 enzymes. As a strong inhibitor of CYP3A4, it also has the potential to interact significantly with other drugs, leading to either increased or decreased plasma levels of those drugs; this can potentially increase their toxicity or reduce their effectiveness.[29]

Although it has been reported that statins are generally safe, they can cause life-threatening conditions at high doses, which can occur when they are used concomitantly with other drugs that increase systemic exposure. Since ITZ increases the AUC values of lovastatin, simvastatin, and atorvastatin by 15-20, 19, and 2.3-3.3 times their original values, respectively, its use with statins is contraindicated.[30]

Elderly patients should be given preference for topical therapy, as well as systemic therapy should only be considered in the cases where topical therapy fails, or the condition is extensive or the recalcitrant.[23]

Expert opinion on concomitant use of ITZ with oral contraceptives

It has been reported that ITZ and oral contraceptives may increase the incidence of 'delayed bleeding' adverse events in women, and hence, they should be used with caution or discontinued altogether.

CURRENT TREND OF ITZ-C AND PROSPECTS OF ITZ-SB

The CDSCO in India has approved multiple strengths of ITZ-SB for the treatment of systemic mycosis over the past 2 years (50 mg, 65 mg, 100 mg, and 130mg). Since ITZ-SB is an advanced version of ITZ-C, all strengths of ITZ-SB have received approval for treating systemic mycosis.[11]

Equivalence data for ITZ-SB and ITZ-C may be the basis for the choice of therapy. Standardization of the appropriate dosing regimen, either BD or OD, for the different strengths of ITZ formulations available, is desirable. A concern was raised regarding the use of Lozanoc® (50 mg BD), which has 80% absorption for action, resulting in underdosing by 15% as compared to Sporanox® (100 mg BD), which has 50%–55% availability for action (despite Lozanoc® being 30% more bioavailable than Sporanox®).

As per the concerns raised by the experts over the availability of different strengths of ITZ and the effects of granule surface coating affecting its bioavailability, it was reported that the amount of coating increases with increasing strengths of ITZ; hence, increased surface coating increases the bioavailability. Furthermore, it was determined that the strength does not affect the bioavailability, but the quality and consistency of the pellet size do; this was deemed to be uniform across all products.

Expert opinion on Fixtral SB

The US-FDA has approved ITZ-C (Sporanox®) only for T. unguium. Conventional ITZ is not approved for dermatophytosis by the US-FDA; however, it is used off-label by most clinicians. The experts stated that AUC/MIC is significant for clinical or laboratory studies, but its relevance at the clinical level is uncertain. It was claimed that the test product (Fixtral SB or ITZ-SB; 100 mg) is therapeutically equivalent to the reference product (Sporanox capsules; 100 mg×2 capsules) for each MIC level. The experts have further mentioned that as per their clinical experience, ITZ-SB 50 mg BD was not clinically equivalent to ITZ-C 100 mg BD and that the dosage also varied based on the body weight of the patient. Hence, it was suggested that data should be collected as per clinical experience and validated. Fixtral SB can be prescribed in women, patients who are drug naïve, and lean patients, as well as those with comorbid conditions. The major benefit of the Fixtral SB formulation is that it is manufactured in-house in the company's laboratory with innovative technology. The experts suggest a lower stock-keeping unit for ITZ-SB, that is, 50 mg and 65 mg, rather than 100 mg, so that it can be titrated well. Future directions include drug promotion and establishing the clinical efficacy of the drug through robust trials.

CONCLUSION

The APSG™ technology is an innovative technology that enhances the solubility and maximizes the bioavailability of poorly soluble drugs, such as ITZ, and achieves a bioequivalence of 200 mg of ITZ-C with 100 mg of ITZ-SB. The APSG™ process uses a drug–polymer solution and spray granulation technology to create amorphous solid dispersion powders. This results in the formation of microencapsulated ITZ distributed within a polymer matrix. The selected polymer exhibits fast solubility in intestinal pH (>5.0), facilitating the rapid and complete release of the drug for optimal absorption. The APSGTM technology is reliable and allows for the development of control strategies to ensure consistent product performance.

The super bioavailable formulation, ITZ-SB (100 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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