Review Article

Super Bioavailable Itraconazole and Its Place and Relevance in Recalcitrant Dermatophytosis: Revisiting Skin Levels of Itraconazole and Minimum Inhibitory Concentration Data

Abstract

Itraconazole, is the most commonly prescribed oral antifungal agent in India, and has a low minimum inhibitory concentration as compared to other oral antifungals, and in conjunction with the markedly high skin levels, the drug should have a predictably good clinical response which is not the consistent experience of clinicians . Probably the variation in pelletization parameters might affect the bioavailability of the drug and consequently affect the serum levels. The maximum bioavailability of conventional itraconazole is 55 percent, which is neither consistent nor predictable. However, the novel itraconazole (Super bioavailable Itraconazole) with targeted drug release in the small intestine has predictable serum levels with minimum interindividual variability, which could make it a potentially useful drug in recalcitrant dermatophytosis.

Keywords: *Bioavailability, conventional, itraconazole, minimum inhibitory concentration, pharmacokinetics, recalcitrant dermatophytosis, resistance, super bioavailable, targeted drug release, variability, Trichophyton, Tinea corporis*

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Background And The Prevalent Use of Itraconazole

While India is still battling the scourge of recalcitrant dermatophytosis, it is pertinent to re-examine the four main aspects that may determine the recalcitrance[1]; these are the species and its reported resistance, the minimum inhibitory concentration (MIC) levels, the serum levels of drugs and the skin levels of the antifungal drugs [Figure 1]. Many studies from India have shown that there is increasing clinical resistance to terbinafine, griseofulvin, and fluconazole with a proportionately high MIC, and thus the most effective oral drug remains itraconazole (ITZ).[2-5] The species and its variations based on changing assessment methods have as yet not shown any clinical utility beyond academic and taxonomical discourses.[6] Minimum inhibitory concentration (MIC) levels to ITZ have been low across the seminal studies. Hence, the intrinsic variations in species probably do not matter as far as ITZ is concerned.[4,5,7-11] [Table 1] Even if we focus on virulence factors and the purported role of the species on the immune response, this would be relevant only if the MICs are high to ITZ. Thus as a corollary, with low MIC the dermatophyte species will not perpetuate to express its "pathogenicity" and cause any significant clinical consequence if the MIC to ITZ remains low. Also, there is no study from India to suggest any specific virulence factors linked to the currently prevalent strain. The refrain of "resistance" to ITZ is without any scientific basis as no mutation to the drug has been reported in the dermatophyte species. If there were a resistance, the MIC levels would have been much higher than the prevalent values.[8,12,13] Also, the immunological compromise of topical steroids[12] does not persist for a long time if stopped, and we do not feel that is the overriding cause, though this is a focus of active research.

This brings us to the issue of skin and serum levels. It is of paramount importance to appreciate that it is the skin levels of ITZ that is important for its action in dermatophytosis, and this has been studied over various time frames levels in various sites with a marked increase in sebum rich

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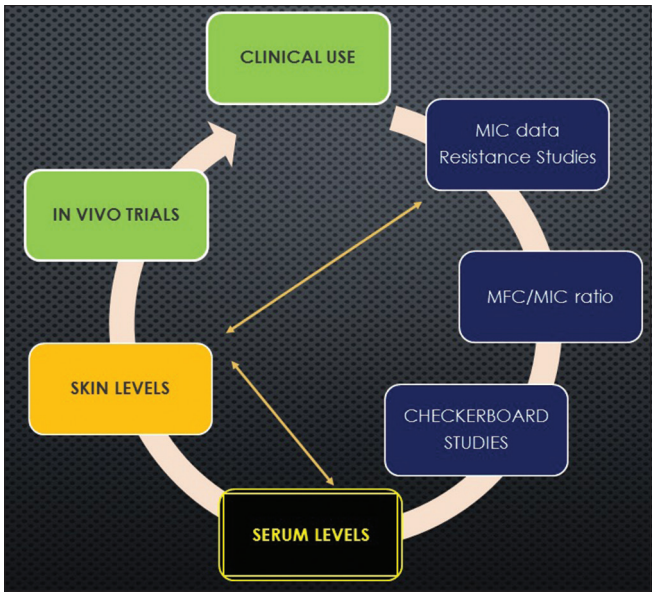

Figure 1: Steps that determine clinical use of Antifungal drugs including itraconazole. The Laboratory data is based on minimal inhibitory concentration (MIC), Minimal fungicidal depend on the concentration (MFC)/ MIC ratio and checkerboard studies. The serum levels bioavailability which should be correlated with skin levels of the drug. The skin levels should be higher than the MIC levels for consistent with clinical efficacy serum. Superbioavailable Itraconazole would lead to consistently uniform levels which are higher than conventional itraconazole and the skin levels enhanced than the prevalent MIC levels in India this should translate into clinical efficacy

sites [Figure 2]. A logical method of predicting response is to compare this with the current MIC levels.[14] Hence if the MIC levels are low as compared to the skin levels of the drug[4,5,7-11] [Table 1], there should be a predictably good clinical response. If we consider the serum levels of 0.34 μg/mL and the corresponding skin levels, which range from 1.467 μg/gm in the beard region to 0.587 μg/gm in the back with a 100 mg dose of ITZ given for 4 weeks,[15] the levels in the skin are much higher than prevalent MICs (0.474 μg/mL).[4,5,7-11] [Table 1]

The variation in skin levels is due to the drug being lipophilic, and with a corresponding higher level in sebum rich areas. Considering this and the propensity for most clinicians to prescribe an enhanced dose of 200 mg twice daily (BD), almost all patients should respond to the drug. The evident clinical failure or slow response brings us to the issue of lack of adequate serum levels, which is related in the first place to quality variations,[16] on which the serum levels are dependent. This has been shown by two papers that highlighted the role of adequate number, size, layering, and the type of pellets, which is the basis of the applicability of pelletization[17,18] and, as a corollary, the bioavailability of ITZ. While certain manufacturers have ramped up the pellet count, it is the thickness of ITZ coating, the number of layers of the active moiety, the polymer used, and the use of dummy pellets that may complicate the bioavailability of brands in India. It is heartening to note that the industry has tacitly accepted

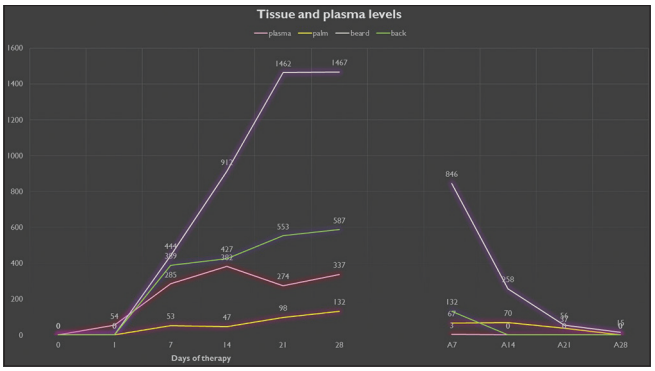

Figure 2: Pharmacokinetic profile of oral itraconazole in human skin 100 mg × 4 weeks and after stopping therapy. This reveals that the level of the drug varies with a higher level in the sebum rich areas of skin as compared to plasma but the levels in the skin are consistently higher than serum levels with a peak level at 21 days (Plasma levels μg/mL; skin levels μg/gm)

this fact, and this is one of the fundamental premises of utility of the super bioavailable itraconazole (SUBA™ ITZ) in the Indian context.

Super Bioavailable (SUBA™) Itraconazole

Itraconazole is a weakly basic molecule with a very erratic absorption pattern leading to wide fluctuations in its blood concentration.[19] For any drug to produce an optimal clinical effect, its absorption and hence bioavailability should be high with minimal interindividual variability. This was the intent behind the development of SUBA™ ITZ. It contains a solid dispersion of ITZ in a uniform non-pellet formulation containing a pH-dependent polymeric matrix-hypromellose phthalate (HPMCP), which enhances its dissolution and intestinal absorption[20]; therefore, the formulation exhibits greater bioavailability than the innovator C-ITZ. A comparison of SUBA™ ITZ and C-ITZ is given in the table and highlights the advantages of the former drug formulation.[17,19-30] [Table 2]

Lindsay *et al*. demonstrated that with the same equivalent doses of 200 mg BD, SUBA™ ITZ achieved therapeutic concentrations more quickly, achieved significantly higher mean trough levels, and much less inter-patient variation in trough levels (60% with C-ITZ versus 35% with SUBA™ ITZ).[30] Abuhelwa *et al*. also demonstrated a 21% lower variability in the bioavailability of SUBA™ ITZ versus C-ITZ.[20] However, the authors observed a similar reduction in bioavailability (27%) with food for both SUBA™ ITZ and Sporanox (innovator C-ITZ capsule formulation). Authors noted that the food decreased the rate and extent of drug absorption, leading to a decrease in bioavailability and a lower absorption rate compared to fasted state irrespective of the formulation. Similarly, Lindsay *et al*.[29] had also observed modestly lower total and peak ITZ exposures when it was administered under fed conditions than in the fasted state. The variation of absorption with food on C-ITZ is important as the drug is currently recommended to be taken in a fed state. Yun

Table 1: An overview of salient studies with the MIC values to select antifungal drugs published by Indian Institutes

STUDY NO	AUTHOR, YEAR[4,5,7-11]	ISOLATES TESTED	MIC 90 (µg/mL)				
			TRB	ITZ	FLU	GRI	KTZ
1	Rudramurthy *et al*., 2018	88, *T. interdigitale*	4	0.5	16	64	0.5
2	Khurana *et al*., 2018	64, *T. interdigitale*	32	1	32	4	0.5
3	Mahajan *et al*., 2017	50, *T.mentagrophytes*	0.03	0.03	16	4	0.03
4	Dabas *et al*., 2017	37, *T. interdigitale*	0.375	0.042	-	0.375	-
5	Pathania *et al*., 2018	50, *T.mentagrophytes*	8	0.5	16	128	-
6	Singh *et al*., 2019	129, *T. mentagrophytes*-interdigitale complex	32	1	32	4	2
7	Shaw *et al*., 2020	498, *T. mentagrophytes*-interdigitale complex	8	0.25	16	32	0.5
Mean MIC 90				0.474			

MIC: minimal inhibitory concentration; TRB: terbinafine; ITZ: itraconazole; FLU: fluconazole; GRI: griseofulvin; KTZ: ketoconazole

Table 2: A comparison of SUBA™ ITZ and C-ITZ highlighting the advantages and drawbacks of this technology

Parameters assessed	Super bioavailable Itraconazole	Conventional itraconazole (C-ITZ)
Formulation	Non-pellet formulation[20]	Pellet formulation[17]
Polymeric matrix	pH-dependent-Hypromellose phthalate (HPMCP)[20]	HPMC (hydroxypropyl methylcellulose)
Site of absorption	Intestinal absorption[20]	Restricted to the stomach[22-24]
Targeted drug release	Yes	No
Bioavailability	Higher than C-ITZ[21]	55% bioavailability[19]
Interaction with food	27% reduction in bioavailability with food (administered in fed/fasting state)[20]	Bioavailability with food highly variable (administered in fed state)
Inter-subject variability	21% less variable between subjects as compared to C-ITZ[20]	Inter-subject variability higher
Effect of antacids	22% increase in total plasma levels with co-administration of omeprazole[29]	C-ITZ capsules with omeprazole reduces its Cmax by 66% and mean area AUC by 64%[25-28]
Equivalent Dose	50, 58 ,65 mg[21,30]	100 mg

et al. reported an increase in bioavailability of ITZ after a bread meal while a decrease after a rice meal due to a rise in gastric Ph lowering its absorption. Thus the amount of fluid administered with the drug, variation in gastric Ph among individuals in both fasted as well as fed state, the fat content of the meal are significant parameters responsible for the contradictory results.[31,32]

The US-FDA has approved SUBA™ ITZ for blastomycosis (pulmonary and extrapulmonary), histoplasmosis (including chronic cavitary pulmonary disease, and disseminated non-meningeal histoplasmosis), and aspergillosis (pulmonary and extrapulmonary in patients intolerant or refractory to amphotericin B therapy).[19] The distribution, metabolism, and excretion are similar to that of C-ITZ, as are the contraindications, drug-drug interaction, precautions, and the adverse effect profile.

In essence, SUBA™ ITZ has predictable serum levels, which obviates the quality concerns of pellets to a large extent and achieves consistent high serum levels without interindividual variation, which would translate to higher skin levels.[20] While the drug does not have US-FDA approval for dermatophytosis, this is possible as in the West, terbinafine remains an effective drug. Here it is pertinent to point that the Central Drugs Standard Control Organisation (CDSCO) in India has not approved C-ITZ for dermatophytosis[33], which is contrary to widespread use at a dose (200, 400 mg) higher than the approved dose of 100 mg capsule. The US FDA approval for C-ITZ is 200 mg (100 mg × 2 capsules) for dermatophytosis, and a dose of 50 mg BD of the SUBA ITZ may be useful to 100 mg BD of C ITZ. clinically as it has been shown to be the equivalent in clinical studies [Table 2]. At the time of writing this manuscript, only one company in India has been able to show equivalence with laboratory data to both the innovator C-ITZ molecule and the international SUBA™ ITZ; hence a certification from CDSCO/Drug Controller General of India (DCGI) is mandated before any such claims are entertained as the molecule is expensive than C-ITZ in India.[34]

Limitations of SUBA™ ITZ

An important issue with SUBA™ ITZ is that this formulation has not been used in dermatophytosis, and it can be argued that as in India, many C-ITZ clinicians (indiscriminately) prescibe 200 mg BD; the serum levels of C-ITZ would be much higher, translating into higher skin levels. This premise is incorrect as, beyond 200 mg dose, there is a hepatic saturation of the drug, and thus the levels do not rise consistently.[17,18] Also, there is a marked inter-individual variation in levels even with C-ITZ, and beyond a predetermined pellet number (≥560), the excess pellets (in a 200 mg capsule) tend to congeal

and with the dynamic transit time in the stomach do not have proportionately higher bioavailability in vivo.[17,18] This is in the GIT important as *in vitro* data do not account for the transit time and thus the levels that are achieved are not representative of *in vivo* levels .Unless there is data to show that 200 mg BD of C-ITZ is superior to the US FDA approved dose of 200 mg (100mg BD), the premise of its superiority is.

It can be logically presumed that the low MIC levels to ITZ [Table 1], its apparent clinical failure despite the exponential increase in skin levels compared to the serum levels [Figure 2], point towards inconsistent serum levels of the existing brands in India. Herein, lies the place of SUBA™ ITZ, which achieves higher consistent serum levels and this formulation might translate into enhanced efficacy for recalcitrant dermatophytosis.

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Conflicts of interest

There are no conflicts of interest.

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