Itraconazole: What Clinicians Should Know?

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Abstract

Our purpose in assembling this paper is 2-fold. First, we hope to review in-depth the properties on itraconazole pellet-capsules and what clinicians should know when considering oral itraconazole and discuss the potential value of treating superficial dermatophyte infections with oral antifungal therapy. Second, we hope to address some of the concerns of the recent epidemic of chronic recalcitrant widespread dermatophytosis in India, with emphasis on better treatment but also considering some of the necessary prophylaxis hygiene measures. An in-depth review of itraconazole (as pellet-capsules), a triazole antifungal will be presented with focus on the pharmacokinetic properties which lead to the development of the 1-week pulse dosing for skin and nail infections. Finally, recommendations for best usage of itraconazole pellet-capsules for management of dermatophytosis will be summarized in this paper.

Keywords: Dermatophytosis, itraconazole, onychomycosis, recalcitrant skin infections

BACKGROUND

In the recent years, there seems to be an epidemic of chronic recalcitrant widespread dermatophytosis in India and perhaps broader.[1,2] Although the recently published reviews from scientific leaders in India, suggest that such cases are about 3%–5% (sometimes up to 10%) of outpatient clinic cases,[2] in a country of 1.3 billion population, even such small prevalence can result in huge healthcare and economic impact. Increasing resistance against terbinafine has led to consider oral itraconazole currently as an important drug for treatment of such widespread dermatophytosis. This clinical scenario of fungal menace and the clinical appropriate use of itraconazole prompted us to have an updated paper on what clinicians should know on the use of itraconazole pellet-capsules for such difficult to treat cases.

INTRODUCTION

Itraconazole, synthesized in 1980 as a triazole antifungal, is the result of target-oriented drug design following a screening research program aiming into the development of a broad-spectrum antifungal agent with documented in vivo activity against dermatophytes (including Microsporum canis), yeasts (Candida spp.), and molds (including Aspergillus). Globally, itraconazole is available in oral (capsule and solution) and intravenous formulations and had been used worldwide for about 30 years. With more than 250 million treated patients with itraconazole (internal data), its safety profile is well defined and usually has been found to be well tolerated. However, in India, as only itraconazole 100 mg capsule formulation is approved by the national drug regulatory authority (Central Drugs Standard Control Organization),[6] this article will focus on review of the same. Furthermore, the data discussed in this review were generated in various clinical and nonclinical studies of originator itraconazole oral formulation and may not be fully applicable to other oral itraconazole formulations available in the market.

PHARMACOLOGY OF ITRACONAZOLE

Each capsule of itraconazole contains 100 mg itraconazole coated over pellets (pellet-capsules). Itraconazole is a weak base and is only ionized at a low pH; hence, gastric acidity is required for drug dissolution and adequate absorption. Consequently, itraconazole capsules should be taken
Itraconazole is lipophilic and extensively (99.8%) bound to plasma proteins. The protein or tissue bound concentration of itraconazole is more clinically relevant than the free drug concentration.\textsuperscript{[7]} Despite high plasma protein binding, itraconazole concentrations within tissues such as kidney, liver, bone, stomach, spleen, and muscle are high. Itraconazole also accumulates in tissues that are prone to fungal infections, such as the skin, nails, lungs, and female genital tract.\textsuperscript{[9]} The extensive protein binding of itraconazole ensures that its concentration at the site of infection remains higher than the corresponding plasma concentration for several days. Based on this property of itraconazole, it is recommended to use in pulse therapy for the management of dermatophytosis including onychomycosis.\textsuperscript{[10]}

**Skin kinetics of itraconazole**

The pharmacokinetics of itraconazole in the skin is unique. In the study conducted by Cauwenbergh \textit{et al.}\textsuperscript{[11]} to determine the itraconazole’s kinetic profile in the skin, upon giving itraconazole 200 mg daily for 7 days, plasma steady state was reached within 4 days after the start of therapy [Figure 1]. Steady-state peak plasma levels ranged from 498 to 646 ng/ml. Itraconazole levels in the sebum became measurable after 4 days of drug intake and were 5–10 times higher than the corresponding peak plasma levels. Importance of sebum secretion was evident by the presence of itraconazole in the beard region which have much higher level of sebum secretion. Similar results of itraconazole level were seen in the stratum corneum of the back due to even distribution of sebum and sweat glands. One week after the end of therapy, the sebum still contained therapeutic levels of itraconazole (271 ng/g), but sebum levels were no longer detectable 2 weeks after the end of therapy. Itraconazole became detectable in sweat (5 ng/ml) 24 h after the first intake of medication and were measurable as long as plasma levels of itraconazole were measurable (that is, until 1 week after the end of therapy). Itraconazole levels in the palmar stratum corneum became detectable for the first time after 7 days of therapy (77 ng/g), levels which were substantially lower with 200 mg dose compared to the body regions with sebaceous glands, and they persisted during the follow-up period of 2 weeks after the end of therapy because of the thickness of the stratum corneum.\textsuperscript{[11]}

These findings indicate that the major routes of itraconazole delivery into the skin likely are passive diffusion from the blood in the keratinocytes (with strong adherence to keratin) and excretion by sebaceous glands. Excretion in sweat, the major route of delivery for Griseofulvin to the skin,\textsuperscript{[12]} seems to be a minor one for itraconazole.

**Nail kinetics of itraconazole**

Nail kinetic studies conducted by Matthieu \textit{et al.}\textsuperscript{[13]} indicate that when itraconazole reaches the nail, fast diffusion occurs in the nail bed and itraconazole appears in the distal part of fingernails after 7 days of oral therapy. Itraconazole seems to reach the nail not only through incorporation into the nail matrix but also by diffusion from the nail bed into the nail plate. Drug levels accumulate and remain in the nail for 6–9 months after stopping therapy (6 months for fingernails up to 9 months for toenails).\textsuperscript{[14]} With two to three 1-week pulses of 400 mg, itraconazole levels were above the 400 ng/ml for the whole period of nail renewal. These levels are indeed required as it was demonstrated that patients who were cured had higher levels compared to the noncured patients.\textsuperscript{[15]}

The affinity of itraconazole toward keratinous tissue and the ability to stay there for long even in the absence of measurable plasma levels makes itraconazole appropriate for treating superficial fungal infections. Furthermore, itraconazole is not redistributed into the systemic circulation after incorporation in the epidermis and the nails and it will persist in the stratum corneum, nail matrix, nail plate, and nail bed after therapy is discontinued, depending on the site of infection while complete clearance in the systemic blood circulation is about 8–10 days after stopping treatment. This explains its utility as 1-week pulse therapy.\textsuperscript{[10]}

**Pharmacodynamics of Itraconazole**

\textit{In vitro and in vivo} (Figure 1)

Several pharmacological studies of itraconazole have been conducted in humans and animals. Studies in animal models of superficial and systemic mycoses have demonstrated excellent activity for itraconazole when administered orally at doses of 5–10 mg/kg, against \textit{Trichophyton rubrum}, \textit{Trichophyton mentagrophytes}, \textit{Candida albicans}, \textit{Aspergillus} spp. In dogs and rats, no significant toxic effects were seen at doses of up to 40 mg/kg.\textsuperscript{[16,17]}

With itraconazole, routine \textit{in vitro} testing methods, such as broth dilution, provide reproducible endpoints and minimum inhibitory concentration (MIC) values closer to the clinical response. Itraconazole showed a broad \textit{in vitro} activity and low MIC against most isolates of \textit{C. albicans} and many other \textit{Candida} spp., excellent activity against dermatophyte...
fungi (Trichophyton spp., Epidermophyton floccosum, Microsporum spp.) and for most isolates of Aspergillus spp., dematiaceous hyphomycetes, dimorphic pathogens, and Cryptococcus neoformans [Figure 2].

Important to note is that fungal strains, particularly dermatophytes, and strains among Aspergillus spp. and dematiaceous hyphomycetes are exquisitely susceptible to the fungitoxic action in vitro, rather than merely being slowed and this is referred to the minimum fungicidal concentration (MFC) needed to kill the fungi. Levels are higher than MIC levels [Table 1] and need to be maintained ≥24 h to be effective. It is therefore essential to ensure appropriate levels in the target organs (preferably MFC) for the right time to ensure optimal efficacy and avoid resistance development.

### Ex vivo

The study with ex vivo skin stripping’s, after administration of oral itraconazole (200 mg OD or 400 mg daily for 7 days), showed excellent fungitoxic activity against T. rubrum and C. albicans. The level of inhibition was highest and most prolonged with the 400 mg dose for 2–3 weeks after last dose, followed by the 200 mg dose.

Based on the PK/PD properties, pulse therapy is still recommended. Pulses of 1 week itraconazole can deliver adequate drug levels in the target organs. Based on the international clinical trials, 200 mg dose for 1 week is the appropriate treatment for glabrous tinea infections (tinea corporis/tinea cruris), 400 mg for 1 week for palmo/plantar skin infections, and 2–3 pulses for nail infections. No pulse data are available for tinea capitis infections where continuous dosing for 4 weeks is still the recommended treatment duration.

### Clinical Studies Overview

From the global database where all international studies have been analyzed and summarized, 1 week pulse of itraconazole 200 mg for tinea infections of the skin and 400 mg for tinea pedis/manus resulted in a clinical response rate of over 90% with mycological cure rates above 80%. Similar cure rates are observed for finger and toenail infections with 2 pulses for fingernails and 3 pulses for toenails of 1 week 400 mg [Table 2]. Depending on the severity of the toenail infections (e.g., severe hyperkeratosis, total nail involvement, slow nail growth), clinicians may decide to use combination treatment with topical or applying mechanical/chemical nail avulsion to increase success.

### Treatment Failure to Itraconazole

Few strains of dermatophytes show primary in vitro resistance against some azoles. However, there are more reports on treatment failures of dermatophyte infections which may rather be caused by insufficient bioavailability of the used antifungal agents. Insufficient bioavailability of itraconazole can result due to concomitant use of antacids or when used in immunocompromised patients.

A few clinical cases of aspergillosis are reported globally were replacement of innovator itraconazole (Sporanox®) capsule with generic itraconazole capsules resulted in treatment failure due to inadequate plasma levels of itraconazole and even development of resistance in one case.

A reported case of onychomycosis treated with generic itraconazole resulted in no clinical response, whereas the same case responded well to innovator itraconazole (Sporanox®) capsule. A randomized two-way crossover study conducted to compare both the formulation, indicated that the relative bioavailability of generic itraconazole to innovator itraconazole was only 3.5 ± 2.8% (range: 0.5%–8.2%), indicating that itraconazole

### Table 1: Minimum inhibitory concentrations and minimum fungicidal concentrations of itraconazole for dermatophytes (adapted from Hazen 1998)

| Species (number of isolates) | MIC (µg/mL) | MFC (µg/mL) |
|-----------------------------|-------------|-------------|
| Trichophyton mentagrophytes (6) | 0.003–0.03 | 0.007–>2 |
| Trichophyton rubrum (7) | 0.003–0.01 | 0.25–>2 |
| Trichophyton tonsurans (5) | <0.004 | 0.0625–>1 |
| Microsporum canis (2) | <0.004 | 0.5–2 |

MIC: Minimum inhibitory concentration, MFC: Minimum fungicidal concentration

![Figure 2](Image): The in vitro activity of itraconazole as determined in brain–heart infusion broth (adapted from Van Cutsem et al.)
was hardly or not absorbed from the generic formulation.\[^{28}\] These reports suggest that proper quality of oral itraconazole and bioequivalence proven according to stringent criteria are essential to maintain the adequate blood level of itraconazole and prevent resistance and treatment failure to itraconazole.\[^{27}\]

**Manufacturing Challenges of Itraconazole**

As per the biopharmaceutics classification system, itraconazole is an example of a Class II compound (low solubility and high permeability) and thus suffer from poor aqueous solubility. This results in poor dissolution rate in the GI tract and may compromise oral bioavailability.\[^{29}\] Therefore, the enhancement of the dissolution rate of itraconazole after oral administration was one of the most challenging aspects when the pellet-capsule formulation of itraconazole was developed. The solubility and bioavailability of itraconazole were increased by some complex processes and technology.

Itraconazole (Sporanox\textsuperscript{®}) was developed with multiparticulate drug delivery systems, namely, beads/pellets. Each itraconazole (Sporanox\textsuperscript{®}) 100 mg capsule contains about 460 mg of coated pellets filled in a capsule of size 0. Itraconazole is mixed with a hydrophilic polymer (hydroxypropyl methylcellulose [HPMC]) and many small sucrose beads having diameter of 600-700 µm are coated with this mixture. The drug-polymer ratio (40:60) is a critical and crucial factor for optimum solubility and bioavailability. A secondary coating by PEG20000 layer to prevent agglutination in the gastrointestinal tract is applied afterward.\[^{30}\] Core particles need to have a diameter between 600 and 700 µm for having optimal drug availability and making the coating process feasible. Lesser diameter particles cannot be coated properly while larger diameter particles offer lesser surface area for drug dissolution.\[^{31}\]

Itraconazole is in a molecular dispersion in amorphous HPMC polymer in the capsule. The fast-dissolving polymer provides a supersaturated solution of itraconazole, from which enhanced absorption can be expected.\[^{32}\] Itraconazole 100 mg pellet-capsule is the optimal size that still allows easy swallowing. Attempts had been made to make itraconazole 200 mg capsule. However, with the same pellet size and technology, this required a much large capsule (size 000) [Figure 3] which would be very difficult to swallow leading to noncompliance. Change in the pellet size by altering the drug-polymer ratio or removing the PEG20000 layer leads to instable formulations and negatively impacted the bioavailability.\[^{33}\] The decision was taken not to develop a 200 mg capsule due to the known limitations (instability, larger capsule size, increased risk for agglutination, and gel formation) Therefore, original itraconazole brand is not present in a capsule formulation beyond 100 mg dosage. However, US-FDA has approved an itraconazole 200 mg tablet based on melt extrusion which uses a different technology for the treatment of onychomycosis of the toenail caused by T. rubrum or T. mentagrophytes.\[^{34}\]

**Safety and Tolerability of Itraconazole**

During short-term itraconazole therapy, adverse events occurred in 7.0% of patients with superficial mycoses. The most frequently reported adverse events were nausea (1.7%), headache (1.0%), and abdominal/epigastric pain (0.8%). During long-term therapy in patients with systemic mycoses, most of whom had a major underlying pathology and multiple concomitant treatments, the incidence of adverse events was higher (16.2%). The most frequently reported adverse events were of gastrointestinal origin (6.1%), with nausea (2.0%) and epigastric pain being the most common.\[^{35}\]

During long-term treatment of onychomycosis, the observed percentage of increases in liver function tests (3.5%) was not higher than the background incidence, and generally, these incidences resolved after discontinuation of therapy. However, it is advisable to monitor liver function during the treatment for periods longer than 30 days.\[^{36}\] A few cases of hypokalemia have been observed during long-term therapy at high doses (>400 mg/day).\[^{36}\] An important risk consideration is for patients with a history of cardiac history/failure where the

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**Table 2: Cure rate of itraconazole on 1 week dosing for skin infections and nail infections**

| Disorder                        | Dosage (mg) | Number of patients (n) | Clinical success (%) | Mycological success (%) |
|---------------------------------|-------------|------------------------|----------------------|-------------------------|
| Tinea corporis/cruris           | 200         | 1027                   | 93.5                 | 84                      |
| Tinea pedis/manus palmoplantar type | 400         | 435                    | 93                   | 78                      |
| Pityriasis versicolor           | 200         | 1052                   | 96.5                 | 88                      |
| Cutaneous candidiasis          | 200         | 104                    | 96.2                 | 81.5                    |
| Fingernail infection           | 400         | 443                    | 94.6                 | 95.6                    |
| Toenail infection              | 400         | 1938                   | 84.5                 | 74.4                    |

*Sporanox\textsuperscript{®} Clinical trial data on file*
benefits of treating should outweigh the risk of congestive heart failure.\[37\] A few cases of torsade de pointses had been reported when itraconazole was used in comedication with terfenadine in the past.\[38\] This resulted in a “black box” warning label of itraconazole and restricted its use in patients on drugs at risk for serious cardiovascular events.\[39\]

Itraconazole must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the fetus. In animal studies, itraconazole has shown reproduction toxicity. During postmarketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations. A causal relationship with itraconazole has not been established.\[22,40\] Clinical data on the use of itraconazole capsules in pediatric patients are limited. The use of itraconazole capsules in pediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks. When indicated, in children, the recommend dose is 3–5 mg/kg/day.\[39\] In clinical trials, includingss pediatric patients, the nature of adverse reactions in pediatric patients was similar to that observed in adult subjects, but the incidence was higher in the pediatric patients.\[22\]

### Drug interactions

When prescribing itraconazole, the clinician must be aware of the potential for drug-drug interactions. Azole derivatives are metabolized in the liver through the cytochrome P450 3A4 enzyme system and consequently, itraconazole may affect or be affected by other drugs metabolized by the same enzyme system. A good drug history is essential to rule out any possible unwanted drug interaction as coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects, and/or sudden death. Drugs that are contraindicated or recommended for use with caution in combination with itraconazole are listed in Table 3.\[41\]

### Expert Opinion for More Recalcitrant and Widespread Infections

As no large-controlled studies are available for recalcitrant and widespread skin infections currently observed in India, the discussion and experience among the Indian dermatologists resulted in the recommendation to give longer treatment, either continuous therapy up to 3–6 months of 100 mg daily or more 1 week intensive therapy of 200 mg daily. Based on the PK/PD and clinical experience with current recalcitrant skin tinea infections from the Indian dermatologists, it indicates toward (a) to give longer treatment until complete cure and (b) in case of itraconazole being considered, repeat intensive therapy over 2–3 months after the initial 1 week dosing of 200 mg daily until complete healing as a good alternative. In addition, to prevent recurrences or relapse, a maintenance regimen should be considered either with topical or oral antifungals. A maintenance regimen with oral itraconazole (200 mg the first 2 days of each month for 4–6 months following the initial pulse treatment) was shown to be effective as prophylaxis in seborrheic dermatitis and patients with Malassezia positive atopic dermatitis of face and neck;\[42\] however, no studies are available with oral itraconazole to demonstrate control of relapses of widespread recalcitrant dermatophytosis. Topical antifungal supplementation is also a useful approach for improving cure rates and helping to control relapses. It is essential to control for relapses of these difficult recalcitrant infections and also to prevent infections in other family members. It is recommended to implement a holistic approach to treat the family.

Additional measures are also important to achieve and maintain success of antifungal treatment. A few of these

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**Table 3: Itraconazole drug interactions: Recommended usage of other drugs**

| Cautions | Contraindications |
|----------|-------------------|
| Alprazolam | Gefitinib | Ramelteon | Astemizole | Lurasidone |
| Aripiprazole | Haloperidol | Rapamycin | Bepridil | Methylergometrine |
| Atorvastatin | Imatinib | Reboxetine | Cisapride | Nisoldipine |
| Bortezomib | Imidafacin | Risperidone | Colchicine | Oral midazolam |
| Brotizolam | Indinavir | Ritonavir | Ergotamine | Oral triazolam |
| Budesonide | Ixabepilone | Saquinavir | Felodipine | Pimozide |
| Buspirone | Lapatinib | Sildenafil | Fosoterodine | Quinidine |
| Busulfan | Maraviroc | Solifenacin | Irinotecan | Ranolazine |
| Ciclesonide | Methylprednisolone | Tacrolimus | Ixabradine | Sertindole |
| Cyclosporine | Midazolam IV | Tadalafil | Lercanidipine | Simvastatin |
| Dexamethasone | Nadolol | Temsirolimus | Lovastatin | |
| Docetaxel | Perospirone | Tolterodine | |
| Erlotinib | Ponatinib | Trimetrexate | |
| Fesoterodine | Quetiapine | Verapamil | |
| Fluticasone | Oxybutynin | Vinca alkaloids | |

**Note:** IV: Intravenous
measures should be as follows. All family members with a similar infection should be treated. In case, there is no infection of a family member, the prophylactic use of a topical antifungal can easily be applied to the whole body including the hair and nails can help prevent infections of further family members. Ketoconazole 2% solution could be a good option as it has a strong affinity for keratinous tissues and has an excellent antidermatopyle efficacy.[40] However, I should be applied in such a way that irritation should not occur. Other hygiene measures such as washing clothes at temperature >60°C, ironing, hanging the clothes reversed on sunlight, clean the floors with agents that kill or eliminate the fungal spores.

Thus, important antifungal molecules such as itraconazole should be appropriately and judiciously used in patients of dermatophytosis in the dosages as recommended by experts. In addition to this, other measures as outlined above should be taken to tackle the menace of superficial fungal infection in India.

Financial support and sponsorship
Nil.

Conflicts of interest
Dr. Sushil Pande has received honoraria from Johnson and Johnson Pvt. Ltd., India, Dr. Ute Richarz in an employee of Janssen Global Services, Switzerland, Dr. Piet De Doncker is an employee of Janssen Research and Development, Belgium, Dr. Nishant Garodia is employee of Janssen Pharmaceuticals, India.

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