

## **Pharmacokinetic Optimization of Itraconazole Therapy**

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## **Abstract**

*Itraconazole is a broad-spectrum triazole antifungal with clinically useful activity against both superficial and systemic mycoses including Aspergillus species. In the past, the role of itraconazole in the treatment of invasive aspergillosis was limited by the erratic bioavailability of the oral capsule formulation in immunocompromised patients. The reformulation of itraconazole with hydroxypropyl- $\beta$ -cyclodextrin into an oral and intravenous solution, however, has revitalized the role of this antifungal in the treatment of fungal infections in critically-ill patients. Even with these new formulations, predicting an appropriate dosage of itraconazole for the individual patient remains problematic due to the considerable intra- and inter-patient variability of itraconazole pharmacokinetics. This monograph reviews key biopharmaceutical and pharmacokinetic concepts clinicians need to understand in order to individualize and optimize itraconazole dosing in a patients with invasive fungal infections.*

## **Introduction**

Itraconazole (Sporanox<sup>®</sup>) is a triazole antifungal that has been in clinical use for over a decade. Initially introduced as a capsule formulation, itraconazole was marketed for the treatment of both superficial (onychomycosis) and systemic (blastomycosis, histoplasmosis) fungal infections. Itraconazole was also the first azole antifungal agent approved for the treatment of invasive aspergillosis (IA) in patients who were refractory to, or intolerant of amphotericin B therapy (Denning *et al.*, 1994). Early use of itraconazole for serious fungal infections, however, was limited by variability in the absorption and plasma drug concentrations that were achieved with the capsule formulation (Boogaerts and Maertens, 2001a). This variability was not problematic for the treatment of superficial fungal infections, as itraconazole accumulated to high concentrations in the skin and nail beds (De Beule and Van Gestel, 2001). For systemic fungal infections, however, consistent plasma concentrations are necessary for clinical efficacy (Poirier and Cheymol, 1998). In early studies examining the use of itraconazole capsules for antifungal prophylaxis in persistently neutropenic patients, > 40% of patients had low or undetectable plasma trough itraconazole levels after two weeks of daily dosing (Boogaerts *et al.*, 1989; Glasmacher *et al.*, 1998). Not surprisingly, breakthrough fungal infections were common in these patients with suboptimal itraconazole plasma levels (Boogaerts *et al.*, 1989).

To overcome the pharmacokinetic deficiencies of the capsule formulation, two new formulations of itraconazole (oral solution and IV formulation) were developed. The improved absorption and consistent plasma levels achieved with these new formulations has opened up the possibility of using itraconazole in more seriously-ill patients with invasive fungal infections. However, predicting an appropriate dosing strategy for itraconazole in the critically-ill patient remains a challenge due to the dose-dependent pharmacokinetic profile, potential for multiple drug interactions, and substantial inter-patient variability in drug metabolism. To use itraconazole effectively, clinicians must understand key differences between the three itraconazole formulations, and recognize common “pharmacokinetic pitfalls” that can lead to sub-optimal drug levels. This monograph will provide a practical review of the biopharmaceutical differences between the three itraconazole formulations, summarize common dosing strategies including conversion from IV to oral therapy, and discuss the role of plasma drug level monitoring in the monitoring and dosing of itraconazole.

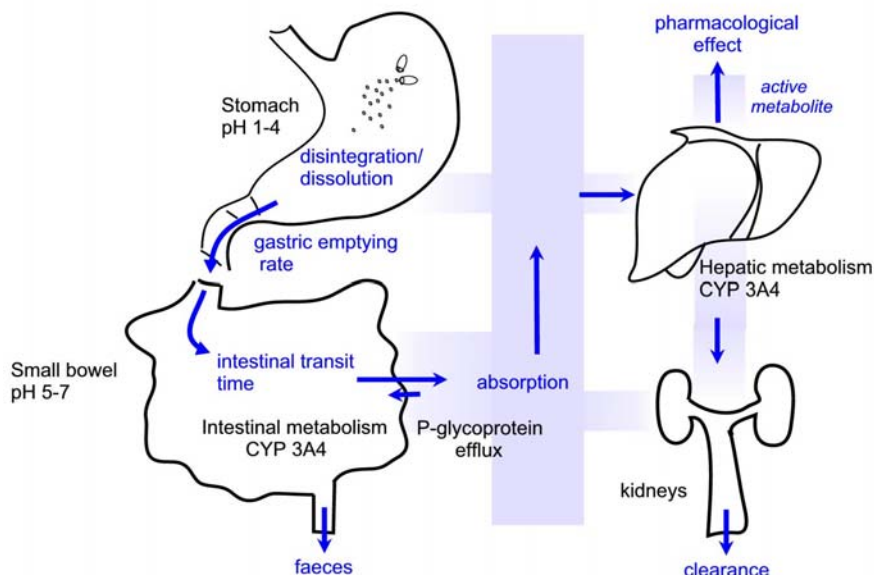
## **Biopharmaceutics of itraconazole**

### *The Problem of Adequate Dissolution*

Itraconazole is a synthetic triazole antifungal agent that is highly lipophilic and virtually insoluble in water. It is an extremely weak base ( $pK_a = 3.7$ ) that is ionized only at low pH, such as that found in gastric fluid. Therefore, one of the initial problems associated with the oral administration of itraconazole is that of insufficient dissolution in the stomach before the drug is delivered to the intestinal lumen for absorption (Figure 1). Dissolution of itraconazole is optimal at a pH 1-4, with impaired absorption occurring above these pH values (Lange *et al.*, 1997). Gastric emptying rate also plays an important role in the absorption of solid itraconazole dosage forms. Generally, slower emptying rates will be associated with

greater itraconazole dissolution and absorption. For this reason, it is recommended that itraconazole capsules be taken after a full meal for optimal dissolution.

Figure 1. Gastrointestinal Dissolution and Absorption of Itraconazole

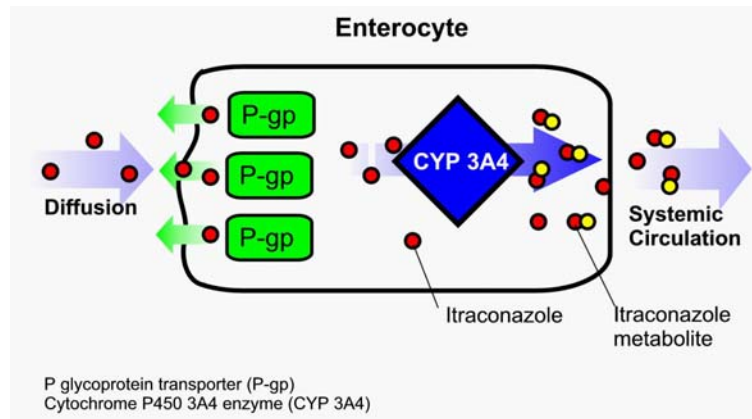


### The Problem of Intestinal Absorption

Once the drug is delivered in solution to the intestinal lumen, it is susceptible to the actions of a variety of plasma membrane transporters and metabolic enzymes located in intestinal enterocytes. Two mechanisms have been identified as important modulators of pre-systemic clearance/metabolism. P-glycoprotein (P-gp) is a versatile drug transporter found on the apical (luminal) plasma membrane surface of mature enterocytes, where it functions as a “detoxification” pump that expels xenobiotics from the cytoplasm to the exterior of the cell (i.e from the enterocyte back to the intestinal lumen) (Hall *et al.*, 1999). Itraconazole is both an inhibitor and substrate of P-gp. Hence, the ultimate effects of P-gp on intestinal absorption of itraconazole can be mixed, or change over a period of prolonged exposure to itraconazole. Moreover, there is significant person-to-person variation in the intestinal expression of P-gp transporters; up to 4-fold variation in healthy volunteers to 10-fold variations in P-gp pump expression in medical patients (Hall *et*

*al.*, 1999). Patient diet, underlying disease, drug therapy, and genetics all play a role in P-gp expression (Hall *et al.*, 1999). This variability in P-gp expression probably accounts for some of the intra and interpatient variability of itraconazole absorption.

Figure 2. Intestinal Transport/Metabolism of Itraconazole



The second major mechanism of pre-systemic clearance of itraconazole involves intestinal metabolism by cytochrome P450 3A4 isoenzyme (CYP 3A4), which results in the production of both inactive and active metabolites. Hydroxy-itraconazole is an active metabolite of CYP 3A4-mediated metabolism that can be found in concentrations  $\sim 2x$  that of the parent drug, which suggests a major contribution to the overall mycological activity observed during itraconazole therapy (Poirier and Cheymol, 1998). Like P-gp, itraconazole is both a substrate and inhibitor of CYP 3A4 (Gubbins *et al.*, 2001). The close cellular location of P-gp and CYP 3A4 in enterocytes and the overlapping substrate specificity suggest that the two mechanisms work synergistically to form a coordinated intestinal barrier to a variety of xenobiotics such as itraconazole (Hall *et al.*, 1999). Additionally, expression of CYP 3A4 in enterocytes exhibits similar intra and interpatient variability as seen with P-gp and is not under coordinate regulation of CYP3A4 expression in the liver (Lown *et al.*, 1994). Therefore, it is difficult to predict what effects increased drug doses, concomitant medications, or chemotherapy-induced changes in the intestinal lumen may have on the absorption of itraconazole. Studies examining

plasma itraconazole trough levels with successive cycles of chemotherapy have shown that drug concentrations can either increase or decrease during each course of chemotherapy depending on the patient (Heykants *et al.*, 1989). These changes in bioavailability could not be predicted from previous treatment courses/chemotherapy cycles with itraconazole.

#### *Itraconazole Distribution and Elimination*

Itraconazole that is absorbed into the systemic circulation is highly bound to red blood cells and plasma proteins (> 99%) (Poirier and Cheymol, 1998) Therefore, unbound concentrations of itraconazole in the body fluids (CSF, eye, saliva) are low in relation to plasma concentrations. However, tissue concentrations of itraconazole are generally 2-10 fold higher than concurrent plasma concentrations (Heykants *et al.*, 1989). Especially high concentrations of itraconazole can be found in vaginal tissue and the horny layer of the nails, where drug levels remain elevated more than 10 days after drug is cleared from the plasma (Heykants *et al.*, 1989).

Systemically-available itraconazole is extensively metabolized in the liver to both active and inactive metabolites, which are subsequently cleared by the kidneys. Approximately 50% of the drug is removed by first-pass metabolism in the liver (and intestinal lumen) resulting in a maximal oral bioavailability of approximately 50% (Heykants *et al.*, 1989). However, this first-pass metabolism can be reversibly saturated with increasing itraconazole doses resulting in an absolute bioavailability > 80% (Stevens, 1999). The terminal elimination half-life of itraconazole ( $t_{1/2\beta}$ ) after a single oral dose is approximately  $24 \pm 9$  hours and 14 hours for the active hydroxy metabolite. Both active and non-active metabolites are excreted in the urine. Due to self-inhibition of its own metabolism, the half life of itraconazole generally increases to over 30 hours in patients after one week of therapy (Hardin *et al.*, 1988).

Approximately 3-18% of itraconazole (non-absorbed) is passed unchanged in the faeces (Poirier and Cheymol, 1998).

Over a dosing range of 100-400 mg/day, itraconazole displays dose-dependent pharmacokinetics in healthy adults. However, at doses > 400 mg/day plasma concentrations are higher than might be expected from dosing because of saturation of itraconazole CYP 3A4 metabolism in the gut and/or liver (Poirier and Cheymol, 1998). Plasma AUCs are generally 4-5x higher after 2-3 weeks of therapy compared to those achieved after a single dose (Heykants *et al.*, 1989).

### **Key Pharmacokinetic Differences of the Itraconazole Formulations**

#### *Capsules*

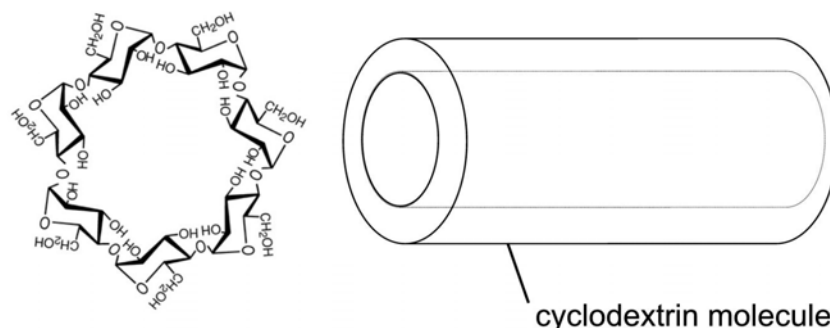
As mentioned previously, one of the major drawbacks to administering itraconazole via the oral route lies in the poor solubility (dissolution) of the antifungal. The first strategy used to overcome this poor solubility involved the synthesis of antifungal-coated sugar spheres in a capsule formulation to maximize the available surface area for dissolution of itraconazole. This approach had limited success, however, in patients with drug or disease-related gastric hypochlorhydria (pH > 4); a common condition in seriously-ill patients. In some cases, capsule absorption could be improved if the capsules were administered with an acidic beverage (i.e cola or juice) in divided doses (Poirier *et al.*, 1997).

#### *Oral Solution*

A more successful approach towards the improvement of itraconazole absorption involved the incorporation of itraconazole into a 40% hydroxypropyl- $\beta$ -cyclodextrin (cyclodextrin) vehicle. Cyclodextrin is a ring of substituted glucose molecules that form a cylindrical structure with a hydrophobic inner pocket and a

hydrophilic exterior. Lipophilic molecules such as itraconazole can be incorporated into this lipophilic pocket to improve their water solubility (Figure 3).

Figure 3. Structural representation of the cyclodextrin molecule (adapted from references (Stevens, 1999; De Beule and Van Gestel, 2001)



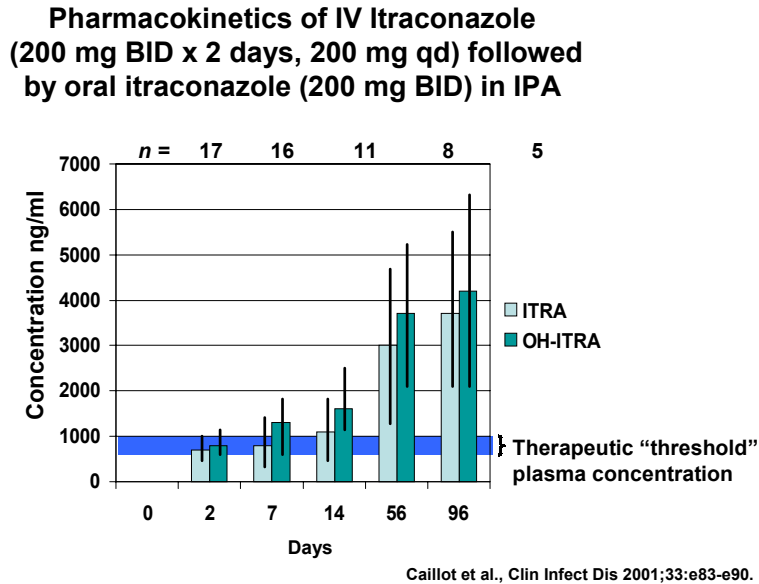
With the incorporation of itraconazole into the cyclodextrin vehicle, the problems of incomplete dissolution at high gastric pH are avoided. This was evident from pharmacokinetic studies performed in normal volunteers, which demonstrated 30% higher  $AUC_{0-24}$  for the oral solution under fed conditions, and 60% higher  $AUC_{0-24}$  when the cyclodextrin/itraconazole solution is administered under fasting conditions (Van de Velde *et al.*, 1996). Therefore, unlike the capsule formulation, itraconazole solution is generally taken on an empty stomach. Less than 3% of cyclodextrin is absorbed from the gut in healthy adults, with 50-60% of the vehicle passing unchanged in the faeces (Stevens, 1999). The remaining cyclodextrin is broken down by gut microflora into constituent glucose molecules, which are then absorbed and metabolized by the liver. Like any polysaccharide, unchanged cyclodextrin passing through the gut stimulates intestinal secretion and gastrointestinal propulsion, thus resulting in nausea and/or osmotic diarrhoea (Stevens, 1999). Cyclodextrin-related gastrointestinal effects generally increase with escalating itraconazole dosages, especially when oral solution doses increase over 400 mg/day (Glasmacher *et al.*, 1999b)

The oral solution formulation of itraconazole is unique in that it achieves high drug concentrations in the oral mucosa and saliva, presumably due to a topical effect of the solution (Mascarenas *et al.*, 1998; Stevens, 1999). These high drug concentrations may persist for up to 8 hours after dosing, thus enabling the use of the oral solution in the treatment of thrush or oral-oesophageal candidiasis. However, high drug concentrations in the saliva often cause alternations in perception and poor appetite in patients (Stevens, 1999). These annoying side effects often make long-term compliance with itraconazole solution problematic.

#### *Intravenous Formulation*

IV administration of itraconazole bypasses problems associated with oral absorption, as well mechanisms of pre-systemic clearance/metabolism in the gut and liver. Not surprisingly, the IV formulation achieves effective levels of itraconazole in the plasma much faster and with fewer side effects than oral administration (Boogaerts *et al.*, 2001c; De Beule and Van Gestel, 2001). It has been suggested that trough plasma concentrations of at least 250-500 ng ml<sup>-1</sup> are necessary for antifungal efficacy (Glasmacher *et al.*, 1996; Glasmacher *et al.*, 1999a). Considering the contribution of the hydroxyl-itraconazole active metabolite, this translates to an "effective" plasma trough itraconazole level of approximately 1000 ng ml<sup>-1</sup> -a concentration that exceeds the minimum inhibitory concentration (MIC) for most *Candida* and *Aspergillus* spp. (Pfaller *et al.*, 2002b). When itraconazole is administered intravenously as loading dose (200 mg q12 x 2 days), this therapeutic level is reliably achieved in most patients within 48 hours (Figure 4)(Caillot *et al.*, 2001).

Figure 4. Pharmacokinetics of IV Itraconazole in Patients with Invasive Pulmonary Aspergillosis.



The rapid attainment of “therapeutic” itraconazole levels in high risk patient populations is a major advantage of the IV versus oral formulations. Oral loading-dose regimens (i.e. 400 mg solution BID x 2 days, then 200 mg BID thereafter) have been proposed that can achieve therapeutic plasma concentrations almost as rapidly as IV dosing. However, these loading regimens are associated with a high incidence (> 35%) of nausea and diarrhoea among patients (Glasmacher *et al.*, 1999b). Moreover, the use of oral loading doses of itraconazole is often not feasible among patients with chemotherapy-induced nausea and vomiting and/or mucositis.

After IV administration of itraconazole, the cyclodextrin vehicle is quickly eliminated unchanged by glomerular filtration in the kidneys (De Beule and Van Gestel, 2001). Following a single intravenous dose of 200 mg IV itraconazole to subjects with severe renal impairment ( $CrCl < 19$  ml/min), clearance of HPCD was reduced 6-fold compared to subjects with normal renal dysfunction (Zhou *et al.*, 1998). Cyclodextrins have been associated in animal studies with toxic effects in the kidney, specifically cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis, and urinary bladder. Hence, use of the IV formulation is not

recommended in these patients even though the clinical implication of cyclodextrin accumulation in the humans is not well understood. In subjects with renal impairment and undergoing hemodialysis sessions three times per week, exposure, in terms of the concentration at the end of infusion, to sulphobutyl ether  $\beta$ -cyclodextrin (SBECD) is higher (455%) in these subjects than in subjects with normal renal function. SBECD is dialyzed at a clearance rate of 55 ml/min. SBECD is used to solubilise voriconazole – little data is available of the clearance of the HPCD vehicle used for solubilising itraconazole. No data is available on clearance by haemofiltration of either vehicle.

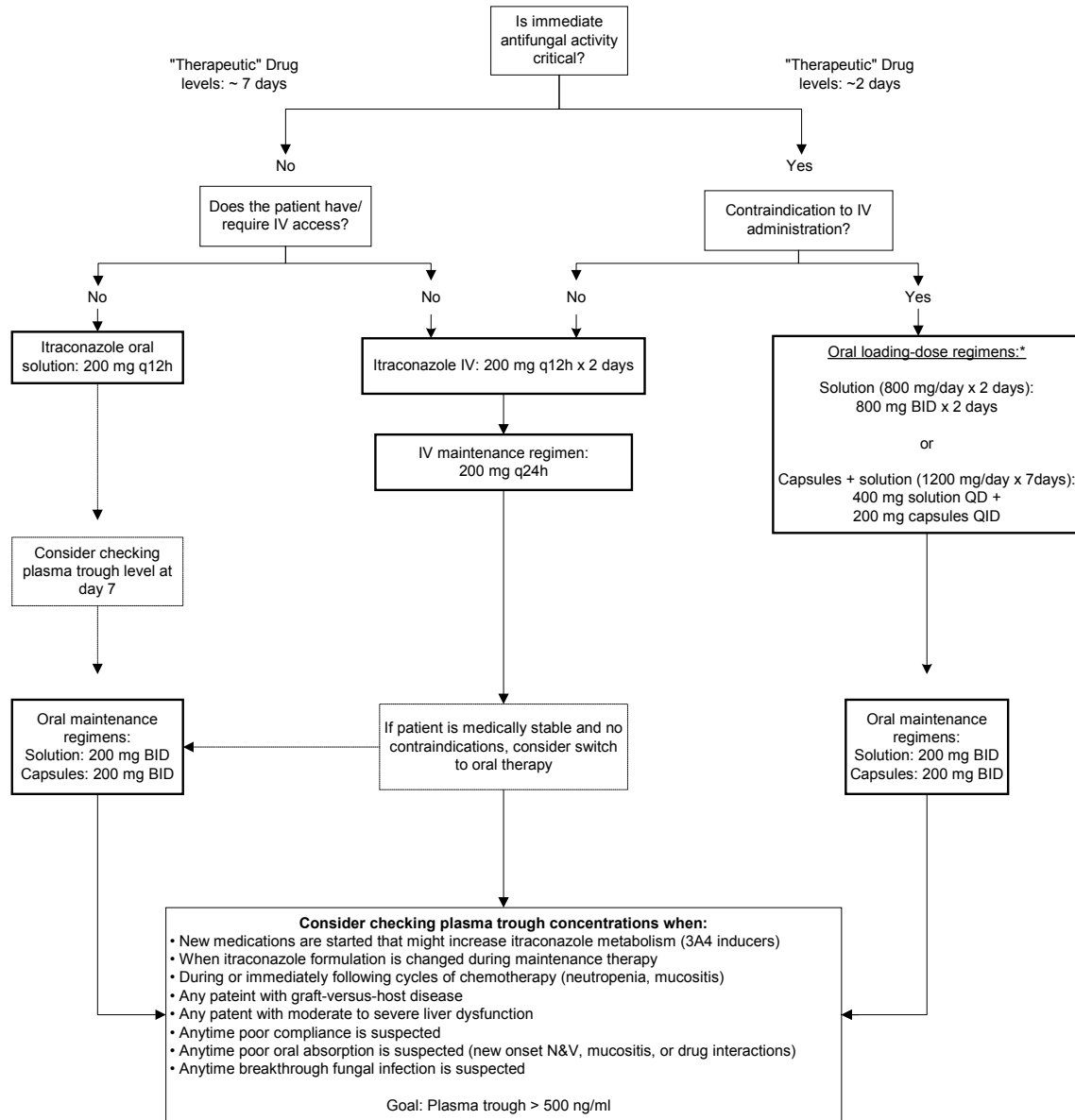
### **Itraconazole dosing strategies, IV/Oral Conversion**

Once steady state concentrations are reached, any of the three itraconazole formulations can be used to maintain plasma concentrations at an effective level provided the patient does not have any contraindications to oral therapy or drug interactions that impair the absorption of the oral formulations. Therefore, the initial factor that needs to be considered when optimizing the itraconazole dosing is that of urgency—namely, how quickly does the patient need “full” therapeutic concentrations of itraconazole? The IV formulation of itraconazole should be used initially in any critically-ill patient or any patient where the full effect antifungal therapy is needed within the next 48-72 hours. Therapy is initiated with a loading dose of 200 mg IV q12x 2 days, then 200 mg/day maintenance dose thereafter (Figure 5). If IV access is not available, clinicians can attempt to administer an oral loading regimen using either the oral solution (400 mg BID x2 days) or a combination of solution and capsules (400 mg solution plus 200 mg capsules QID x 7 days). However, oral loading doses are associated with a higher frequency of nausea and diarrhoea, especially among patients receiving oral solution at doses > 400 mg/day (Glasmacher *et al.*, 1999b). In most cases, IV-administered loading doses will be

the best tolerated and most reliable method for achieving effective plasma concentrations of itraconazole.

Patients initially receiving IV itraconazole can be safely converted to either the oral capsule or solution formulation once they are medically stable and have reliable GI function/absorption. Plasma itraconazole levels will often remain at the same level or even moderately increase after conversion to oral therapy (Zhou *et al.*, 1998; Caillot *et al.*, 2001). Moreover, the daily drug cost for the oral formulations are considerably less than the cost of the IV formulation. Determining which oral formulation can be used in the individual patient depends upon patient-specific risk factors. Although the solution has uniformly better absorption than the capsules and can be taken without food, the solution may be less well tolerated due to nausea, diarrhoea, and persistent taste disturbance. Also the solution formulation is somewhat dilute (10 mg/ml), requiring 2 bottles (150 ml/bottle) per week to take the standard oral maintenance dose of 200 mg BID. Therefore, prolonged or chronic maintenance therapy is often more practical with the capsule formulation. However, the capsule formulation is susceptible to a wider variety of disease and drug-related factors that can decrease absorption. Many patients at risk for invasive fungal infections possess some degree of hypochlorhydria secondary to underlying disease or chemotherapy, and thus are not good candidates for itraconazole capsules. Drug level monitoring can help identify which formulation is appropriate for the individual patient.

Figure 5. Approach to itraconazole dosing in the high-risk patient (Adapted from: Poirier and Cheymol, 1998; Zhou *et al.*, 1998; Glasmacher *et al.*, 1999b; Boogaerts *et al.*, 2001b; Caillot *et al.*, 2001)



\* Oral loading-dose regimens are associated with higher incidence of nausea/diarrhoea, and may not be tolerated in patients who are already experiencing nausea with chemotherapy. Approximately 35% of patients receiving 800 mg/day itraconazole report N&V, diarrhoea. Capsule/solution loading-dose combination appears to have less GI adverse effects (Glasmacher *et al.* 1999).

## **Plasma drug level monitoring during itraconazole therapy**

### *Efficacy monitoring*

Plasma drug level monitoring during itraconazole therapy is clinically indicated in any patient at risk for developing a life-threatening fungal infection, suspected cases of drug failure or infection relapse, or in patients with other risk factors for inadequate plasma drug levels (Figure 5)(1993; Graybill, 1994; Poirier and Cheymol, 1998). As mentioned previously, data from early clinical trials suggest a plasma trough concentration of  $> 250 \text{ ng ml}^{-1}$  of unmetabolized itraconazole is necessary for antifungal efficacy (Tricot *et al.*, 1987; Boogaerts *et al.*, 1989). More recent work by Glasmacher *et al.* have suggested that an itraconazole trough concentration of at least  $500 \text{ ng ml}^{-1}$  is needed to prevent the development of *Aspergillus* infections in neutropenic patients (Glasmacher *et al.*, 1996; Glasmacher *et al.*, 1999a). Considering the contribution of the active hydroxy-metabolite, a plasma trough concentration of  $500 \text{ ng ml}^{-1}$  of parent drug plus metabolite would equate to roughly  $1000 \text{ ng ml}^{-1}$  of itraconazole activity - a concentration that inhibits over 70-90% of common fungal pathogens including *Aspergillus* spp. *in vitro* (Pfaller *et al.*, 2002a; Pfaller *et al.*, 2002b).

A conservative provisional target for patients receiving itraconazole, therefore, would be plasma steady-state trough itraconazole concentrations  $\geq 500 \text{ ng ml}^{-1}$ . Plasma trough itraconazole levels should be determined by HPLC assay, when possible, as interpretation of bioassay results is confounded by the presence of the active metabolite (Law *et al.*, 1999). Measurement of the active hydroxyl-metabolite of itraconazole can also be performed by HPLC, and provides complimentary data in addition to itraconazole levels (Poirier and Cheymol, 1998). However the HPLC measurement of itraconazole is cumbersome (because of the complex and time consuming extraction procedure) and a faster turnaround time can be achieved, with much less precision using bioassay measurements. Using

itraconazole standards the bioassay measurement overestimates itraconazole concentrations by perhaps 5 times, because of the presence of the hydroxyitraconazole metabolite. Excellent correlation can be achieved between bioassay and HPLC if hydroxyitraconazole is used as the standard in the bioassay (Law et al, 1994), but the hydroxyitraconazole metabolite is not easily available. Bioassay may be problematic in the context of combination therapy as well. Generally, the initial plasma concentrations should be determined once the patient reaches steady-state levels (typically 1 week after starting itraconazole therapy). Subsequent plasma level monitoring is then performed on the basis of patient-specific risk factors (Figure 5).

If a plasma itraconazole level measured at steady state comes back low ( $< 500 \text{ ng ml}^{-1}$  by HPLC, or  $\sim 3\text{-}5 \text{ mcg/ml}$  by bioassay) or is undetectable, a repeat plasma trough concentration should be considered if assay turnaround is reasonably short ( $< 7$  days). If a patient has a plasma trough level between  $200\text{-}500 \text{ ng ml}^{-1}$ , dosing adjustment may not be necessary if the level was taken within 1 week of starting oral therapy. However, if the plasma trough concentration is  $< 200 \text{ ng ml}^{-1}$  or undetectable, prescribers should re-administer an IV or oral loading dose of itraconazole and consider possible causes of low itraconazole levels (Table 1).

Table1. Common factors that contribute to sub-optimal itraconazole plasma concentrations.

<b>Problem</b>	<b>Mechanism</b>	<b>Suggested Strategy</b>
<p><b><u>pH interactions (capsules)</u></b></p> <p><b>Drug interactions</b></p> <p>H2 antagonists (i.e famotidine) Proton pump inhibitors (i.e omeprazole) Antacids, didanosine tablets</p> <p><b>Disease state</b></p> <p>Chemotherapy-associated hypochlorhydria Graft-versus-host disease Neutropenia/mucositis AIDS</p>	<p>Decreased dissolution of capsule results in decreased absorption</p>	<p>Change to solution formulation</p> <p>Avoid taking antacids within 2 hours of itraconazole capsules</p>
<p><b><u>Complexation/Chelation Interactions (capsules, solution?)</u></b></p> <p><b>Drug interactions</b></p> <p>Sucralfate Multivitamins Antacids</p>	<p>Complexation with metal ions decreases transport across intestinal epithelium resulting in decreased absorption</p>	<p>Avoid taking binding agent (antacid, multivitamin, etc.) within 2 hours of itraconazole dose</p>
<p><b><u>Increases systemic clearance (all formulations)</u></b></p> <p><b>Drug interactions</b></p> <p>Rifampin Rifabutin Phenytoin Phenobarbital Carbamazepine</p>	<p>Induction of CYP3A4 metabolism results in decrease (30-90%) in plasma C<sub>max</sub>, AUC and t<sub>1/2</sub>. Effects may last 1-2 weeks after drug are stopped</p>	<p>Avoid concomitant use of these agents with itraconazole. May need to switch to amphotericin B or echinocandin</p> <p>If itraconazole must be used with potent inducing agent, prescriber may be able increase dose to compensate for increased clearance (not possible to achieve with rifampin). Dosing should be guided by plasma monitoring.</p>

*Toxicity monitoring*

Common adverse effects of itraconazole therapy include gastrointestinal effects (N&V, diarrhoea), skin rash, and reversible increases in hepatic enzymes (Janssen, 2002). Less common but more severe side effects such as congestive heart failure and idiosyncratic hepatic failure have been reported (Ahmad *et al.*, 2001; Janssen, 2002). Currently, no correlation between plasma itraconazole levels and the frequency or occurrence of toxicity during itraconazole therapy has been demonstrated (Graybill, 1994; Poirier and Cheymol, 1998). Additionally, there are

no reports of using plasma level monitoring to guide itraconazole dosing in patients with moderate to severe hepatic dysfunction. In general, use of itraconazole should be avoided in these with severe liver disease (Janssen, 2002). However, if itraconazole is used, concurrent monitoring of itraconazole levels along with hepatic enzymes and bilirubin may be prudent given that liver disease is associated with multiple factors (e.g. protein binding, drug distribution) that can affect drug distribution and clearance (Lewis and Prince, 2001).

Because itraconazole is substrate of CYP 3A4, concurrent use of itraconazole with potent CYP 3A4 inhibitors (e.g. macrolides, and the protease inhibitors indinavir and ritonavir) could increase plasma drug levels and the likelihood of adverse effects during itraconazole therapy. However, of the few studies that have examined the concomitant use of itraconazole and CYP 3A4 inhibitors, itraconazole levels did not appear to be substantially increased (Auclair *et al.*, 1999; Dresser *et al.*, 2000). Therefore, it appears that itraconazole can be used safely with medications that inhibit CYP 3A4 and plasma level monitoring is not routinely indicated. The long-term consequences of co-administering itraconazole with CYP 3A4 inhibitors, however, has not been examined (Auclair *et al.*, 1999).

## **Conclusion**

For nearly a decade, sub-optimal pharmacokinetics has prevented itraconazole from achieving its full potential in the management of serious fungal infections such as invasive aspergillosis. This is no longer the case, as clinicians now have two new formulations of itraconazole that can rapidly and reliably achieve adequate plasma drug concentrations in the critically-ill patient. Effective use of itraconazole still requires an individualized approach to dosing and careful monitoring. However, the added flexibility of these new formulations are a major advancement for the antifungal armamentarium, and are especially encouraging in the treatment of infections for which few therapeutic options are available.

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