ITRACONAZOLE SOLUTION: SUMMARY OF PHARMACOKINETIC FEATURES AND REVIEW OF ACTIVITY IN THE TREATMENT OF FLUCONAZOLE-RESISTANT ORAL CANDIDOSIS IN HIV-INFECTED PERSONS


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The clinical pharmacology of itraconazole is presented in relation to its use in the treatment of fluconazole-resistant oropharyngeal candidosis. The oral solution is a new formulation of itraconazole in which itraconazole is solubilised with the use of cyclodextrin. This formulation has a higher bioavailability and leads to higher local concentrations in the oral cavity which are advantages over the solid capsule formulation. Literature, in which the use of itraconazole oral solution was described to treat fluconazole-resistant oral candidosis, is reviewed. In about 55% of the patients signs and symptoms of oral candidosis were resolved after treatment with itraconazole oral solution. Although all the reviewed studies lack data to objectively qualify all the included patients as having a fluconazole-resistant candidosis, the authors conclude, that based on the available information itraconazole oral solution 100 or 200 mg twice daily can be effective for fluconazole-resistant oropharyngeal candidosis (OPC) and should be considered prior to salvage therapy with intravenous amphotericin B. The use of itraconazole, however, requires careful monitoring of the patients co-medications for potential serious drug-drug interactions.

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INTRODUCTION

Oropharyngeal candidosis (OPC) is a common opportunistic infection in human immunodeficiency virus (HIV)-infected persons. In the era before highly active antiretroviral therapy (HAART) became available, 80–90% of patients experienced an episode of OPC at some time during the progression of their disease. Although since the introduction of HAART the incidence of OPC has declined dramatically, OPC remains a significant problem [1]. Most patients will respond initially to topical therapy with azoles ( clotrimazole troches) or oral polyenes, such as nystatin or amphotericin B suspension [2]. But topical treatment of oral candidosis has disadvantages such as high relapse rate, unpleasant taste, gastrointestinal upset and reduced effectiveness in advanced stages of HIV-disease. With the introduction in 1990 of fluconazole, an orally absorbed triazole derivative, an effective and well tolerated systemic treatment of oral candidosis in HIV-infected patients became available [3]. Fluconazole has been widely used in HIV-related OPC. Fluconazole-resistance has a low annual incidence of <5% and its occurrence is strongly associated with continuous use and advanced immunosuppression [4]. Intravenous amphotericin B has been an effective salvage therapy in fluconazole-refractory candidosis [2], but this approach is inconvenient and associated with potential toxicities. Experience with itraconazole capsules for fluconazole-resistant OPC has been disappointing [5, 6], but favourable responses have been reported with itraconazole solution [7, 8]. In this article we will review the pharmacological properties of itraconazole in relation to OPC and discuss the results with itraconazole solution in the treatment of fluconazole-resistant OPC in HIV-infected persons.

PHARMACOLOGICAL PROPERTIES OF ITRACONAZOLE

Mechanism of action

Itraconazole is an orally active, broad-spectrum, triazole antifungal agent. The drug is primarily fungistatic at clinically achievable serum concentrations and acts...
Pharmacokinetics

In vitro by impairing the synthesis of ergosterol, an essential component of the fungal cell membrane. In vitro studies have demonstrated that itraconazole interacts with the substrate-binding site of fungal cytochrome P450 (CYP). In this way, itraconazole blocks the, by fungal CYP catalysed, conversion of lanosterol into ergosterol by 14α-demethylase. As a result, lanosterol and other 14α-methylsterols accumulate in the cell membrane, leading to abnormalities in fungal cell membrane permeability and membrane-bound enzyme activity, inhibition of cell growth and ultimately cell death [9].

Pharmacokinetics

Itraconazole is available in three different formulations: a solid formulation consisting of a capsule containing itraconazole-coated sugar spheres, an oral solution in which itraconazole is solubilised with the use of hydroxypropyl-β-cyclodextrin (cyclodextrin) and an intravenous formulation. With respect to the subject of this review, attention is limited to the oral formulations.

Absorption. Since itraconazole is a weak base (pKb = 3.7), it is ionised and water soluble only at low pH. So, in case of the capsule formulation, gastric acidity is required for drug dissolution and adequate absorption. Decreased absorption is observed in the fasting state and in patients with low gastric acidity [10]. It has also been shown, that in persons with the acquired immunodeficiency syndrome (AIDS), the absorption of itraconazole capsules was reduced with 50% compared with healthy persons [11]. Hypochlorhydria and thus a relatively high gastric pH, a frequent complication of HIV infection, may be responsible for this phenomenon [12]. Co-administration of an acidic beverage (e.g. a cola soft drink) is an effective way to improve the bioavailability of itraconazole capsules [13]. Itraconazole is a lipophilic substance, which is practically insoluble in water. It is likely that solubility is the rate-limiting step in itraconazole absorption. To facilitate the solubilisation it is advised to administer the itraconazole capsules shortly after a meal, which leads to improved bioavailability. Compared with administration with food, the bioavailability of itraconazole capsules is reduced by 40% when it is administered under fasting conditions [14]. To improve the absorption and bioavailability of itraconazole an oral solution was developed, in which the drug is solubilised with the use of cyclodextrin. Cyclodextrins are cyclic oligosaccharides that form a cylindrical structure which is hydrophilic on the outside and hydrophobic on the inside. The inside cavity is an ideal place for the lipophilic itraconazole molecule [15]. In the initial studies with the oral solution, itraconazole was administered with food, because of the previous experience with the capsule formulation. Under these conditions the bioavailability of the oral solution was up to 37% higher than that of the capsules, measured by the area under the plasma concentration–time curve (AUC) from 0 to 96 h after the dose [16]. Intake by healthy men of a single dose of 100 mg itraconazole as oral solution after a standardised breakfast, resulted in a bioavailability of 55% compared to a single 100 mg itraconazole dose administered by intravenous infusion over 1 h. Other reports, however, showed that absorption of the solution was faster and better when taken without food. The time to reach the maximum plasma concentration (tmax) was considerably shorter under fasting (1.7 h) than under fed (3.8 h) conditions and bioavailability of itraconazole was 30% higher under fasting conditions [17]. After rapid absorption of the solution, high plasma concentrations are probably achieved by transient saturation of the first-pass effect [17]. The bioavailability of itraconazole oral solution taken in a fasting condition is approximately 60% higher than that of the capsules taken with a meal [18]. The bioavailability of itraconazole oral solution in HIV infected patients is reduced by approximately 20% compared to normal volunteers. The stage of the HIV infection has no influence on the bioavailability [19]. The absorption of cyclodextrin after administration of the oral solution is negligible. Enzymes in the gut such as cyclodextrin transglycosylase convert the cyclodextrin ring into its constituent glucose molecules, which are absorbed and metabolised by the liver. The osmotic activity of cyclodextrin in the intestine, however, may cause patients to experience diarrhoea and other gastrointestinal symptoms [20].

Distribution. Itraconazole is widely distributed, with an apparent volume of distribution of 10.7 l/kg after intravenous administration. The drug is 99.8% bound to plasma proteins, primarily albumin [14]. Tissues such as skin, nails, muscles and liver accumulate large concentrations of itraconazole, while body fluids such as cerebrospinal fluid, eye fluid, saliva and sputum contain low to undetectable amounts [21]. High concentrations of itraconazole, however, have been detected in saliva for up to 8 h after a single dose of the oral solution. Since only itraconazole was detected in these saliva samples without any traces of its main metabolite hydroxyitraconazole, these concentrations are more likely the result of “sticking” of itraconazole to the oral mucosa followed by a slow release into saliva, than of active secretion of systemically absorbed drug by the salivary glands [19]. This hypothesis is supported by the fact that in patients who were concurrently using rifampin and itraconazole oral solution, salivary itraconazole concentrations were detectable until at least 4 h after swallowing the solution while itraconazole was undetectable at any time point in plasma [22].

Elimination. Itraconazole is mainly metabolised in the liver through CYP3A4 into a large number of metabolites. The major metabolite is hydroxyitraconazole, which has a comparable antifungal activity to itraconazole in vitro. Plasma levels of hydroxyitraconazole are about two times higher than those of itraconazole [14]. Elimination of itraconazole is biphasic, with a terminal plasma half life (t1/2) of approximately 20 h after a single dose. At steady state, the terminal t1/2 increases to 30 h, indicating a saturable excretion mechanism [14].
TREATMENT OF FLUCONAZOLE-RESISTANT CANDIDOSIS

In 1997 the National Committee for Clinical Laboratory Standards (NCCLS) approved document M27-A, a widely accepted, standardised and reproducible method for susceptibility testing for fungi [23]. This method defined among others broth-medium, inoculum size, incubation-temperature and duration, endpoint reading and Quality Control isolates. Until that time testing methods were not standardised and antifungal minimum inhibitory concentrations (MIC’s) could vary as much as 50,000-fold by changing the assay conditions [24]. So the wide acceptance of this method was very important. By correlating results obtained by this method with outcome of therapy in both mucosal and bloodstream Candida infections, interpretative breakpoints, for testing the susceptibility of Candida species to fluconazole and itraconazole, based on clinical data, became available (Table I) [25].

These breakpoints, however, place a strong emphasis on interpretation in the context of the delivered dose of the antifungal agent. The category “susceptible, dose-dependent” indicates that maximisation of dosage and bioavailability are crucial for successful therapy. MIC’s in this context should be regarded as an indication for the necessary concentration at the site of infection. A pharmacodynamic study with fluconazole suggests that a dosing regimen designed to maximise the duration of exposure of the infecting organisms to concentrations of two to four times the MIC should optimise the fungistatic activity of the drug [26]. In practice this means, that doses up to 800 mg fluconazole daily may be necessary to treat OPC. So, in order to establish true fluconazole-resistance and to distinguish this from clinical failures due to host (e.g. non-compliance) or medication (inadequate dosage, drug-interactions) related factors, the following information is mandatory: fluconazole dose and duration of therapy, fluconazole plasma concentrations, identification of the Candida species and determination of the MIC. Data about the use of itraconazole oral solution for the treatment of fluconazole-resistant OPC are mostly limited to case reports or abstracts of congress contributions, with insufficient information for critical review. We searched Medline and Pubmed for publications in the period 1990–2001 with “itraconazole (oral) solution” as keyword. We could identify only four, open label, studies, in which itraconazole oral solution was used prospectively to treat fluconazole-resistant candidosis. Data about these studies are summarised in Table II.

Philips et al. [27] studied fluconazole-resistant OPC in 36 HIV-infected patients in the pre-HAART era. Patients were treated with itraconazole oral solution 100 mg twice daily for 2 weeks. Fluconazole-resistant OPC was clinically defined as failed therapy, indicated by the presence of persistent pseudomembranous OPC, despite having received at least 10 days of treatment with fluconazole at a daily dose of at least 100 mg. Of the 36 patients, 22 had used a maximum daily dose of 100–200 mg fluconazole. Fluconazole serum levels obtained at the time of failed therapy (before discontinuation of fluconazole) were determined by a microbiological plate assay. With the same method also itraconazole levels (obtained at steady state, 2 weeks of treatment) were determined. The median (range) fluconazole serum level (n = 21) was 12.9 µg/ml (4.7–40). The reported median (range) itraconazole serum level (n = 21) was 2.5 µg/ml (<0.6–20.8). Clinical response was observed in 22 out of 34 (65%) evaluable cases. Eight patients (24%) had a complete response, defined as resolution of all signs of OPC and 14 patients (41%) had a partial clinical response (improvement). Whether the majority of the included patients can be rightly regarded as infected with fluconazole-resistant Candida remains a matter of debate. MIC’s were not determined conform the approved standardised method and the correlating breakpoints differed substantially from those that are now commonly accepted [25]. With regard to the now accepted fluconazole breakpoint “susceptible, dose-dependent” it is hard to justify that a Candida infection is defined as fluconazole-resistant, when the maximum used daily fluconazole dose was 100 or 200 mg.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Range of MIC’s (µg/ml)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>≥0.125</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>≥8.0</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>≥1.0</td>
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Table I: Interpretative breakpoints for Candida species

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Episodes (n)</th>
<th>Fluconazole dosage</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philips et al. [27]</td>
<td>36</td>
<td>100 mg b.i.d., 14 days</td>
<td>C: 8/34 = 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 14/34 = 41%</td>
</tr>
<tr>
<td>Cartledge et al. [28]</td>
<td>73</td>
<td>200 mg b.i.d., 7 days</td>
<td>C: 44/73 = 60%</td>
</tr>
<tr>
<td>Sng et al. [29]</td>
<td>74</td>
<td>100 mg b.i.d., 14 days (± 14 extra)</td>
<td>C: 41/74 = 55%</td>
</tr>
<tr>
<td>Reyes et al. [30, 31]</td>
<td>36</td>
<td>100 mg b.i.d., 14 days</td>
<td>C: 21/28 = 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 6/28 = 21%</td>
</tr>
</tbody>
</table>

b.i.d.: twice daily; C: complete response/cure; P: partial response/improvement; episode: included/treated episode of fluconazole-resistant OPC
The results of at least the itraconazole determinations should also be questioned. The authors report a median itraconazole level of 2.5 μg/ml. Since they have used a microbiological assay, they have measured the result of the combined antifungal activity of itraconazole plus its active main metabolite hydroxitraconazole. Furthermore, the high itraconazole serum levels do not correspond with the much lower levels (using the same dosage) determined by Reynes et al. using a high performance liquid chromatographic method [19].

Cartledge et al. [28] reported 73 episodes of candidosis in patients who were clinically unresponsive to fluconazole and had fluconazole-resistant isolates in vitro. This study was performed before HAART became available. The patients were treated with itraconazole oral solution 200 mg twice daily for 7 days. Clinical outcome was assessed on day 7 of therapy and classified as response if there were no persistent signs or symptoms of candidosis, and as failure if candidosis was still present. Fluconazole-resistant OPC was defined clinically as candidosis that is persistent despite at least 7 days’ therapy with fluconazole of at least 100 mg per day. In 18 episodes the maximum daily fluconazole dose was 100 mg and in 27 episodes 200 mg. No fluconazole plasma levels were determined. MIC’s were not determined conform NCCLS M27-A. Clinical response was observed in 44 of 73 (60%) episodes. Also in this study the classification of 45 episodes as fluconazole-resistant, while the maximum used daily fluconazole dose was 200 mg and a reliable MIC determination was lacking, remains questionable. But the response to itraconazole solution in relation to the previous used fluconazole dose was the same (approximately 60%) for episodes previously treated with 100, 200 or 400 mg fluconazole.

Saag et al. [29] reported the results of a study in 74 HIV/AIDS patients also performed in the pre-HAART period. Patients were treated with itraconazole oral solution 100 mg twice daily for 2 weeks. Patients who demonstrated an incomplete response to treatment were treated for an additional 14 days (28 days total). OPC was qualified as fluconazole-resistant when the patient had failed to respond to a course of at least 200 mg fluconazole daily during at least 14 days. No fluconazole plasma levels were determined. Itraconazole MIC’s were performed using the standard NCCLS method. Clinical response was defined as no lesions or symptoms at the end of treatment, and was achieved by 41 patients (55%). The median (range) time to response was 7 days [7–28]. Of the clinical responders 24 had itraconazole MIC’s ≤ 0.5 μg/ml and 16 had at least one organism with an MIC = 1.0 μg/ml. Of the non-responders, 17 had itraconazole MIC’s ≤ 0.5 μg/ml and 16 had at least one organism with an MIC ≥ 1 μg/ml. Unfortunately, no itraconazole plasma levels were determined.

Reynes et al. [30] and Mallié et al. [31] reported a study with a.o. 36 HIV-infected patients with fluconazole-resistant OPC. Patients were treated with itraconazole oral solution 100 mg twice a day for 14 days. Fluconazole resistance was defined as persistence of candidosis despite a minimum treatment of 2 weeks with a daily dose of 100 mg fluconazole or more. On the last day of fluconazole treatment, the plasma level of fluconazole was determined by gas chromatography to check compliance, but fluconazole levels and dosages were not specified except that 4 patients had fluconazole plasma levels below 2 μg/ml. Cure was achieved in 21 of 28 evaluable patients (75%) after 2 weeks treatment. Susceptibility testing was done by using the E Test®.

All studies were performed in a period before a reliable method to determine antifungal MIC’s and before the knowledge to interpret the in vitro breakpoints were available. In order to qualify oral candidosis as fluconazole-resistant it is essential to correlate fluconazole dosage with fluconazole plasma concentration (to exclude non-compliance or a possible negative effect of a drug-drug interaction) and to correlate the fluconazole plasma concentration with the MIC (to exclude use of a too low fluconazole dosage). This critical information is incomplete or lacking in the studies mentioned above.

itraconazole safety

Adverse reactions

With the use of itraconazole oral solution, the most frequently reported adverse reactions in the reviewed studies were of gastrointestinal origin, such as diarrhoea, abdominal pain and vomiting. A reversible increase in hepatic enzymes was less frequently reported [27, 29, 30]. Data from the US Food and Drug Administration’s Adverse Event Reporting System suggest that use of itraconazole is associated with congestive heart failure. Recently, details of 58 cases suggestive of congestive heart failure in association with itraconazole were summarised [32]. Labelling of itraconazole has been changed to alert physicians to this finding.

Drug interactions

Itraconazole is mainly metabolised through CYP3A4. Itraconazole is also a potent inhibitor of CYP3A4 and a moderate inhibitor of P-glycoprotein. The liver is the primary site of drug metabolism mediated by the cytochrome P-450 system, but CYP3A4 is also present in the enterocytes of the small intestine [33]. The enterocytes in the intestinal mucosa are also a major site of expression of P-glycoprotein. P-glycoprotein is an ATP-dependent plasma membrane transporter that is an important molecular determinant of oral bioavailability, brain penetration and treatment resistance to several therapeutically used drugs, including HIV protease inhibitors, digoxin, cyclosporin and anticancer agents such as vinca alkaloids, etoposide, paclitaxel and antitumour antibiotics [34–36]. Both CYP and P-glycoprotein can present a barrier to the absorption of orally administered drugs and have a considerable effect on drug interactions. Overlap in tissue distribution and substrate specificity of CYP3A4 and
P-glycoprotein in the gut wall makes it difficult to define the specific mechanisms of drug interactions and to predict the effect on plasma concentrations of certain drug combinations [37].

**Effects of other drugs on itraconazole pharmacokinetics [38–41].** Potent inhibitors of CYP3A4 increase the bioavailability of itraconazole. This has been demonstrated with clarithromycin, erythromycin, indinavir and ritonavir. Rifampicin, phenytoin, rifabutin and isoniazid are enzyme inducing drugs and they reduce the bioavailability of itraconazole significantly. Similar effects should be anticipated with other potent enzyme inducers.

**Effects of itraconazole on other drugs [38–41].** Itraconazole can inhibit the metabolism of drugs metabolised by CYP3A4. This can result in an increase and/or prolongation of their effects and side effects. Examples of drugs which should not be used during treatment with itraconazole are terfenadine, astemizole, cisapride, quinidine, pimozide, HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam and triazolam. Other drugs have also been shown to interact with itraconazole, but can be used concomitantly. The plasma levels, effects or side effects of these drugs should, however, be monitored. If co-administered with itraconazole, the dosage of the following drugs should be reduced if necessary: CYP3A4 plays a major role in the metabolism of the HIV protease inhibitors ritonavir, indinavir, nelfinavir, saquinavir and amprenavir. Ritonavir, indinavir, nelfinavir and saquinavir are also substrates for P-glycoprotein. The effects of itraconazole on protease inhibitor pharmacokinetics probably result from a combination of CYP3A4 and P-glycoprotein inhibition. *In vitro* and *in vivo* inhibition of the metabolism of saquinavir has been demonstrated [42]. The AUC of indinavir increased approximately 25% and the minimum plasma concentration doubled when administered concomitantly with itraconazole (200 mg b.i.d.). Further examples of drugs that require extra attention because of potential higher drug levels when co-administered with itraconazole are coumarin-like drugs (e.g. warfarin), digoxin, calcium channel blockers, buspirone, vinca alkaloids, busulphan, ciclosporin, sirolimus and tacrolimus. The most relevant interactions with itraconazole are summarised in Table III.

**DISCUSSION AND CONCLUSION**

Fluconazole-resistance in *Candida albicans* is a multifactorial process mediated through multiple underlying mechanisms [43]. Resistance can be the result of an alteration of the target enzyme, the cytochrome P-450 lanosterol 14α-demethylase, either by overexpression or as a result of point mutations in the gene that encodes it. The former creates the need for a higher intracellular azole concentration to complex all the enzymes present in the cells, while the latter leads to amino acid substitutions, resulting in a decreased affinity for azole derivatives. Another major mechanism is failure of azole antifungal agents to accumulate inside the cell as a result of enhanced drug resistance.
efflux by plasma membrane transporters. Perea et al. [43] showed that multiple mechanisms of resistance were combined in 75% of the isolates displaying high-level fluconazole resistance. Their analysis confirmed the multifactorial nature of azole resistance and the prevalence of these mechanisms of resistance in Candida albicans clinical isolates exhibiting fluconazole resistance. Overexpression of genes encoding efflux pumps was detected in 85% of all resistant isolates. Alterations in the target enzyme, including functional amino acid substitution and overexpression of the gene that encodes the enzyme, were detected in 65 and 35% of the isolates, respectively.

The fact that itraconazole inhibits (although moderately) the efflux pump P-glycoprotein, makes it, theoretically, an attractive drug to treat fluconazole-resistant OPC. Also, the high tissue concentrations that can be realised and the fact that itraconazole is a very lipophilic drug, which may enhance penetration into the fungus, are favourable characteristics. The solution formulation has distinct advantages over the capsule formulation in the treatment of OPC because it combines systemic activity with local or topical activity (as shown by the long lasting high salivary concentrations). The studies we have discussed all originate from the pre-HAART era. Introduction of HAART has dramatically reduced the incidence of OPC and has limited the possibilities to perform studies with large numbers of patients. The qualification of a large number of patients in the presented studies as having fluconazole-resistant OPC, however, is questionable. Reliable MIC’s for fluconazole were not available and could not be correlated with (in most cases also not available) fluconazole plasma levels to guide dosing or to rule out noncompliance or drug interactions that might lower fluconazole plasma levels. The qualification mainly based on clinical failure to resolve symptoms with, according to the present opinion, often relatively low dosages of fluconazole, remains a weak point of these studies, but probably reflects the limited possibilities of the period in which they were performed. In the mean time this limits the general applicability of the results.

Based on the available information itraconazole oral solution 100 or 200 mg twice daily may be effective for fluconazole-resistant OPC and should be considered prior to salvage therapy with intravenous amphotericin B. The oral solution has distinct advantages over the capsule formulation because of its higher bioavailability and its additional topical effect. The use of itraconazole, however, requires careful monitoring of the patients co-medication for potential serious drug interactions.

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