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Pharmacology of Itraconazole

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Abstract

Itraconazole is a triazole antifungal agent that has a broad spectrum of activity and is well tolerated. Itraconazole is highly efficacious, particularly because its main metabolite, hydroxy-itraconazole, also has considerable antifungal activity.

The original capsule formulation of itraconazole may lead to variability in absorption and the plasma concentration. For the treatment of superficial fungal infections, this is not problematical because itraconazole accumulates at the infection site, making consistently high plasma concentrations unnecessary – a characteristic that has been exploited in the development of a pulse regimen.

Because consistent plasma concentrations are critical for the more serious systemic fungal infections, variable absorption of itraconazole from the capsules limits their application. Moreover, underlying disease processes and medical interventions can reduce absorption from the capsules in some patients with systemic fungal infections. To widen the beneficial application of itraconazole to include such patients, an oral solution and an intravenous formulation were developed. These formulations combine lipophilic itraconazole with hydroxypropyl-β-cyclodextrin, a ring of substituted glucose molecules, which improves the solubility of itraconazole. The enhanced absorption and bioavailability of itraconazole from these new formulations make them ideal for the treatment of systemic fungal infections in a wide range of patient populations. The additional flexibility offered by the different routes of administration also means that itraconazole can be used in patients at high risk, such as children or those requiring intensive care, for whom the capsule formulation may be impractical.

Superficial, subcutaneous and systemic fungal infections cause serious problems in a wide range of people, placing a huge burden on already overstretched healthcare services. Because of the wide range of people who require treatment for fungal infections, it is preferable if the antifungal therapy can be tailored to the precise needs of the individual patient. Itraconazole is available in three formulations [capsules, oral solution and intravenous (IV)], which allows a flexible approach to the treatment of fungal infections.

The capsules have been used successfully for many years, especially for the treatment of superficial and subcutaneous fungal infections. A recent study has shown that itraconazole capsules are also effective at preventing the development of fungal infections, especially in patients with profound and prolonged neutropenia.[1] In some patients, however, itraconazole is absorbed inconsistently from the capsules. After intensive research to improve the absorption and bioavailability of itraconazole, two new formulations were developed – an oral solution and an IV formulation.[2]

To overcome the difficulty of solubilising lipophilic compounds such as itraconazole, hydroxypropyl-β-cyclodextrin (cyclodextrin) is often used. Cyclodextrin is a ring of substituted glucose molecules that form a cylindrical structure which is hydrophilic on the outside and hydrophobic on the inside. This hydrophobic cavity forms an ideal

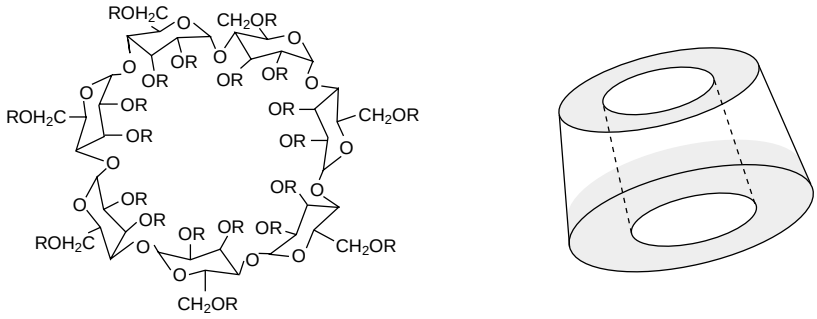

Fig. 1. Molecular structure of cyclodextrin.

chamber for lipophilic molecules, such as itraconazole (fig. 1), thereby improving their solubility.

The pharmacological profile of itraconazole is reviewed in this paper, highlighting the similarities and unique properties of each formulation.

1. Pharmacological Properties of Itraconazole

Regardless of formulation, itraconazole has a broad spectrum of activity; this has enabled it to be used extensively in many different patient groups, generating valuable *in vivo* data. Itraconazole is the only antifungal with oral bioavailability that is effective against *Candida* spp. and *Aspergillus* spp., which are currently the most frequently encountered fungal pathogens.[3]

1.1 Mechanism of Action

Itraconazole inhibits the growth of fungi by interfering with the synthesis of ergosterol, a vital component of the fungal cell membrane (fig. 2).[4] Under normal circumstances, lanosterol, the precursor of ergosterol, undergoes a 14α-demethylation catalysed by fungal cytochrome P450 (CYP). Itraconazole interacts with the substrate-binding site of fungal CYP and blocks this reaction. As a result, lanosterol and other 14α-methyl sterols accumulate in the cell membrane instead of ergosterol. This impairment of ergosterol synthesis leads to abnormalities in the fungal membrane permeability, membrane-bound enzyme activity and the coordination of chitin synthesis.[5,6]

1.2 Distribution

Itraconazole is lipophilic and tightly bound to blood cells and plasma proteins, primarily albumin, leaving only 0.2% of the drug unbound. As expected, therefore, itraconazole concentrations in most body fluids, including cerebrospinal fluid and eye fluid, are low in relation to the plasma concentration.[7] Despite high plasma protein binding, itraconazole concentrations within tissues are considerable, with a large apparent volume of distribution (approximately 11 L/kg). As with all lipophilic antifungal agents, therefore, the protein or tissue-bound concentration of itraconazole is more clinically relevant than the free drug concentration.[8] Tissues such as kidney, liver, bone, stomach, spleen and muscle accumulate large concentrations of itraconazole.

Itraconazole also accumulates in tissues that are prone to fungal infections, such as the skin, nails, lungs and female genital tract.[7] 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. Once equilibrium is established between the tissue and plasma, itraconazole is eliminated from the tissue in line with the usual half-life ($t_{½}$).[8] Small doses of itraconazole given over short dura-

tions are therefore highly effective for the treatment of acute vaginal candidiasis.[9]

The pharmacokinetics of itraconazole in the skin are unique.[10] The major route of delivery is via the sebum, leading to itraconazole concentrations 5- to 10-fold higher than in plasma. This makes itraconazole appropriate for treating dermatological fungal infections, especially those affecting the nails. Soon after the start of therapy, itraconazole can be detected in the distal part of the nail through incorporation into both the matrix and the nail bed.[11] Because itraconazole is not distributed back to the plasma, but remains in the nail until it is shed through normal growth, antifungal therapy does not have to be given continuously.

1.3 Elimination

Itraconazole is metabolised primarily in the liver by a large number of pathways to produce more than 30 metabolites. The major metabolite, hydroxy-itraconazole, reaches higher plasma concentrations than the parent compound and has *in vitro* antifungal activity similar to that of itraconazole.[8,12] Because of the lack of renal metabolism, the dose of itraconazole does not need to be reduced in patients with renal failure and supplementation after dialysis is not necessary.[13]

Elimination of itraconazole is biphasic, with a terminal $t_{1/2}$ of approximately 20 to 24 hours after a single dose. At steady state, the terminal $t_{1/2}$ increases to 30 hours, indicating that the itraconazole excretion mechanism is saturated at clinical doses.[7] Most metabolites are eliminated through the bile and urine but unmetabolised itraconazole is not detected in the urine. Only 3 to 18% of the dose is detected in the faeces.[12]

1.4 Drug Interactions

As a potent inhibitor of the fungal CYP3A isoenzyme, itraconazole also inhibits this enzyme in humans, although with a much lower affinity.[14] It has the potential, therefore, to modify the pharmacokinetics of the many drugs that are metabolised by this route.[15] For example, the plasma concentration of cyclosporin, a drug that is often used in

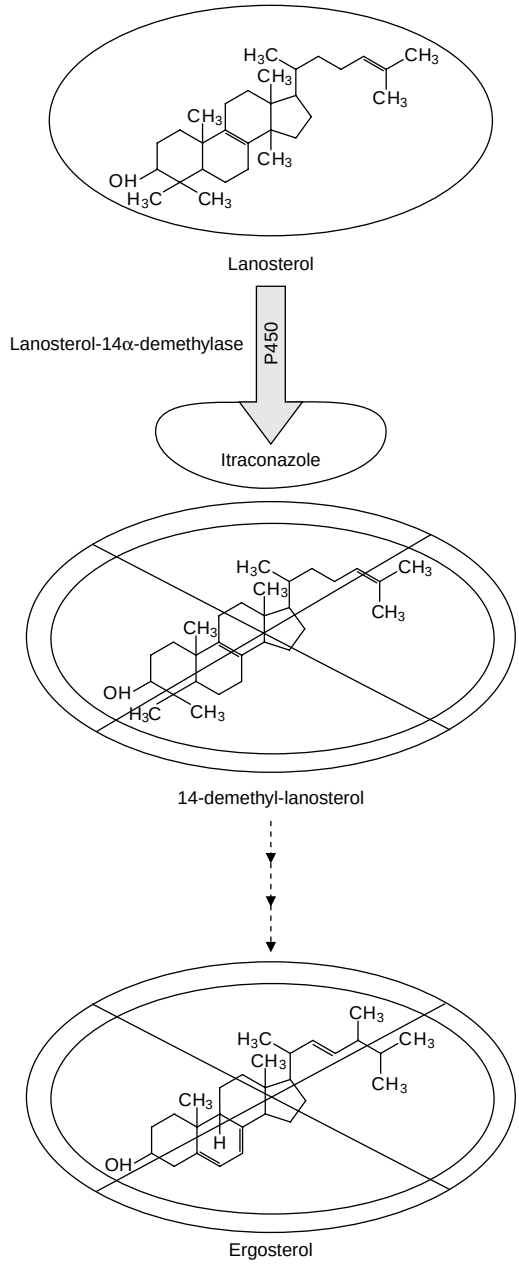

Fig. 2. Mechanism of action of itraconazole: schematic representation of the biosynthesis of ergosterol in fungi, with an emphasis on the step inhibited by itraconazole. **P450** = cytochrome P450.

transplant patients, increases after administration of itraconazole. In some cases, therefore, itraconazole may enable particular concomitant medications to achieve the same therapeutic effects at lower doses as are attained at higher doses without itraconazole, with favourable cost implications.[16] A potentially important interaction between azole antifungal agents and protease inhibitors used for the treatment of HIV has recently been described,[17] which may necessitate dose reduction of both drugs. Despite an increased understanding of the pharmacokinetic mechanism underlying the interaction profile of itraconazole, it is still difficult to predict conclusively the magnitude of these interactions in individual patients. When concomitant medication includes substances that interact extensively with itraconazole, therefore, monitoring of blood concentrations may be useful to ensure optimal efficacy.[18]

2. Capsule Formulation

2.1 Absorption

The absorption of itraconazole from the capsules is perfectly adequate in healthy volunteers and in patients with superficial fungal infections.[19] Indeed, itraconazole capsules are the mainstay of treatment for onychomycosis and tinea infections.[20,21] In some people, however, taking itraconazole capsules on an empty stomach leads to reduced absorption and a decline in clinical response. Given the lipophilic nature of itraconazole, it is likely that solubility is the rate-limiting step in itraconazole absorption. A simple mechanism to facilitate the solubilisation of itraconazole is to administer the capsules shortly after a meal, which leads to optimal systemic availability.[22] Additionally, coadministration of an acidic beverage (e.g. a cola soft drink) is an effective way to improve the bioavailability of itraconazole.[23,24]

Patients with systemic fungal infections may be unable to tolerate solid-dose formulations and, even if they can, absorption may be reduced by low oral food intake, frequent vomiting or difficulty in swallowing the capsules.[25,26] Additionally, in bone marrow transplantation (BMT) patients, graft-versus-host disease, manifesting as a range of upper gastrointestinal abnormalities,[27] diminishes the absorption of itraconazole from the solid formulation.

2.2 Pulse Therapy for Superficial Fungal Infections

Because itraconazole binds preferentially to keratinic tissues (e.g. nails, hair and skin) rather than being distributed back to the plasma, it does not need to be given continuously for the successful treatment of superficial fungal infections. This observation has resulted in the development of itraconazole pulse therapy for onychomycosis, in which the drug is given as a cyclical regimen for 1 week out of every 4.[28] In toenail onychomycosis, for example, clinical cure rates of up to 84% have been observed after only 3 months of pulse therapy with itraconazole capsules (400 mg/day for 1 week per month).[29] Such properties mean that itraconazole capsules are ideal for the treatment of dermatological infections where consistent plasma concentrations are not relevant. Pulse therapy with itraconazole results in higher maximum itraconazole plasma concentrations, but with lower total drug exposure.[30] Additional benefits of pulse therapy include a reduction in drug acquisition costs, enhanced tolerability and an increase in patient compliance.[31]

3. Oral Solution

The combination of itraconazole with cyclodextrin in the oral solution formulation has improved several aspects of the pharmacological profile of this antifungal agent.

3.1 Absorption and Bioavailability

Itraconazole oral solution has an improved bioavailability compared with itraconazole capsules, which makes the oral solution ideal for the treatment of systemic fungal infections. Initial studies of the oral solution were conducted under fed conditions, because previous experience with the

capsules had shown that optimal absorption was achieved in the presence of food. In a comparative study of itraconazole capsules 200mg and itraconazole oral solution 200mg in healthy volunteers, the bioavailability of the oral solution was up to 37% higher than that of the capsule, measured by the area under the plasma concentration-time curve (AUC) from 0 to 96 hours after the dose. The maximum concentrations of itraconazole in plasma (C_{max}), the time to reach C_{max} (t_{max}) and the terminal $t_{½}$ were similar for the capsules and the oral solution.[32]

Subsequent reports showed that absorption of itraconazole oral solution is even better when taken without food, which is more appropriate for at-risk patients. After a single dose of the oral solution, the C_{max} and AUC from 0 to 24 hours after the dose (AUC_{24h}) for itraconazole and hydroxy-itraconazole were significantly higher under fasting conditions than under fed conditions, and the t_{max} was considerably shorter. Consequently, the bioavailability of itraconazole was 30% higher under fasting than under fed conditions.[33] Under optimal conditions, therefore, the bioavailability of itraconazole oral solution is approximately 60% higher than that of the capsules, indicating near complete absorption from this formulation.[32-34] The rapid absorption of itraconazole oral solution can be explained by the absence of the dissolution process on delivery to the stomach because of the non-covalent nature of the itraconazole-cyclodextrin complex. After rapid absorption from the stomach, high plasma concentrations are probably achieved by transient saturation of the first-pass effect.[33]

After administration of itraconazole oral solution, absorption of cyclodextrin is negligible. Enzymes in the gut microflora, such as cyclodextrin transglycolase, convert the cyclodextrin ring into its constituent glucose molecules, which are then absorbed and metabolised by the liver.[35] The osmotic activity of cyclodextrin in the gut, however, may cause patients to experience diarrhoea or other gastrointestinal symptoms.[35]

3.2 Distribution

An additional difference between itraconazole oral solution and capsules is that saliva contains negligible amounts of itraconazole after administration of the capsules, but high concentrations have been detected in saliva for about 8 hours after a single dose of itraconazole oral solution. These data suggest local persistence and the potential for a topical effect of the oral solution on the buccal mucosa. Itraconazole oral solution is therefore appropriate for treating fungal infections of the mouth, including candidiasis,[36] and has shown high efficacy even in fluconazole-refractory disease.[37]

3.3 Pharmacokinetics of Itraconazole Oral Solution in Different Patient Groups

Studies to calculate the bioavailability of the itraconazole oral solution formulation were performed in a variety of immunocompromised patient populations at particular risk of developing fungal infections. To be effective when treating or preventing fungal infections, plasma concentrations of itraconazole must achieve a minimal concentration (C_{min}) at which antifungal activity is maintained. The C_{min} therefore becomes more clinically relevant than the C_{max}. For itraconazole, a C_{min} of at least 250 to 500 μg/L is considered to be desirable, rising to 1 mg/L if the hydroxy-itraconazole plus itraconazole concentration is measured.[12,38] One accepted *in vitro* measure of antifungal activity is estimated as the minimum concentration that is required to inhibit a given percentage of the fungi (MIC) and depends on the particular fungal organism. Although the *in vitro* MIC of an antifungal agent has been criticised as an unreliable reflection of efficacy *in vivo*, the relationship between MIC and treatment success has been used to develop guidelines for interpretive breakpoints, which allow the MIC to be used in a clinically relevant manner (table I).[39] These guidelines use three categories to describe the response of *in vitro Candida* isolates to two antifungal azoles. Two of the categories, susceptible and resistant, are

Table I. Interpretive minimum inhibitory concentration (MIC) breakpoints for itraconazole in the treatment of candidal infections[a]

	Range of MICs (μg/L) per category		
	susceptible	susceptible (dose-dependent)	resistant
Itraconazole	≤125	250-500	≥1000

a Adapted from Rex et al.[39]

consistent with the terms used in the traditional breakpoint method. However, the third category, susceptible (dose-dependent), is used in place of the more traditional 'moderate' or 'intermediate' susceptibility, because of the potential for raising the dose of the azole to achieve effective plasma concentrations at the site of the infection.[39] The interpretive breakpoints shown in table I were derived from data on the treatment of mucosal candidiasis and, as such, may differ for other fungal infections.

When the technique of *in vitro* susceptibility testing is used, which provides MIC results, itraconazole performs well against a wide range of clinical and environmental fungal isolates (table II). In some cases, however, an organism may appear to be resistant to itraconazole *in vitro* even though itraconazole is clinically effective *in vivo*. For example, for *Sporothrix schenckii* the MIC_{90} of itraconazole is 4000 μg/L, but clinical reports show that itraconazole is an effective treatment for sporotrichosis. Furthermore, practice guidelines issued by the Infectious Diseases Society of America recommend itraconazole as the treatment of choice for fixed cutaneous, lymphocutaneous or osteoarticular sporotrichosis.[43]

Many different patient groups require treatment with antifungal agents, so general conclusions about the pharmacokinetics of itraconazole formulations are difficult to make.

3.3.1 Patients with HIV Infection

The enhanced absorption achieved with the solubilised formulations of itraconazole is particularly useful in AIDS patients.[44] In patients with advanced HIV infection, itraconazole plasma concentrations were significantly higher with the oral solution than with the capsules after treatment with itraconazole 200mg twice daily for 7 days (1326 μg/L versus 741 μg/L; $p < 0.05$).[45] In both groups, however, the plasma concentrations of itraconazole were lower than those reached in healthy volunteers with capsules (1960 μg/L)[46] or with the oral solution (2053 μg/L).[34] These results agree with those of earlier studies, which showed a 50% reduction in the absorption of itraconazole capsules in people with AIDS compared with healthy people.[47] Hypochlorhydria, a frequent complication of HIV infection, may be a factor in reducing the absorption of itraconazole capsules.[48,49] Importantly, however, itraconazole absorption after administration of itraconazole oral solution to patients with advanced HIV leads to effective C_{min} levels after 4 days and steady state after 9 to 15 days. The bioavailability of itraconazole oral solution is not affected by the level of gastric acidity,[50] making this formulation particularly suitable for patients who may have hypochlorhydria or achlorhydria. Although people with HIV are not a homogeneous group, the pharmacokinetics of itraconazole

Table II. *In vitro* spectrum of activity of itraconazole[a]

Species	MIC_{90} (μg/L)
Moulds	
Absidia corymbifera	500
Aspergillus flavus	250
Aspergillus fumigatus	500
Cladophialophora bantiana	120
Exophiala dermatitidis	500
Fonsecaea pedrosoi	250
Fusarium solani	>16000
Phialophora parasitica	2000
Rhizopus arrhizus	2000
Scedosporium apiospermum	4000
Sporothrix schenckii	4000
Yeasts	
Candida albicans	310
Candida parapsilosis	150
Candida tropicalis	1250
Candida glabrata	310
Candida krusei	150[b]
Cryptococcus neoformans	150[b]

a Adapted from Johnson et al.,[40] Carrillo-Muñoz et al.,[41] and Verweij et al.[42]

b MIC_{50}.

MIC = minimum concentration required to inhibit a given percentage of the fungi.

oral solution are not modified by the stage of HIV infection.[36]

The tolerability profile of itraconazole oral solution in people with HIV is good regardless of the stage of HIV infection. The somewhat unpleasant taste of itraconazole oral solution may lead to problems of noncompliance but, generally, patients report only mild and transient adverse gastrointestinal experiences, including nausea, diarrhoea, vomiting and abdominal pain.[36,37] It is likely that these adverse events are related to the osmotic effect of cyclodextrin.[35] In a trial of itraconazole oral solution for the treatment of oropharyngeal candidiasis in HIV-positive patients, only 7.7% (6 of 78) patients discontinued therapy because of adverse events, which included just two patients (2.6%) with gastrointestinal effects thought to be related to the active treatment.[37]

3.3.2 Bone Marrow Transplant Recipients

In patients receiving allogeneic bone marrow transplants, antifungal agents are generally given for a period before transplantation and continued until the patient is no longer neutropenic. Because of the additional risk of graft-versus-host disease, these patients can benefit from prolonged antifungal therapy. Studies in which itraconazole oral solution 400mg was given once daily for 7 days before the transplant have shown that an adequate C_{min} of at least 250 μg/L was reached 1 day before transplantation (i.e. after 6 days of itraconazole therapy) in 54% of the study population and by 1 day after transplantation (i.e. after 8 days of itraconazole therapy) in 72% of patients.[51] Alternatively, antifungal therapy can be started after transplantation. The decision about when to start antifungal prophylaxis depends on the type of transplant, the nature of the underlying disorder and a clinical assessment of risk for each individual patient.

After autologous BMT, a C_{min} of at least 250 μg/L was achieved with itraconazole oral solution (5 mg/kg/day) between day 1 and day 8 of itraconazole prophylaxis.[52] Recipients of autologous bone marrow transplants have particular difficulty in absorbing drugs because of chemotherapy-induced epithelial damage. Despite this, itraconazole oral solution achieves the target plasma concentrations in this patient group because of its cyclodextrin formulation.

Some recipients of autologous bone marrow transplants receiving itraconazole oral solution report adverse effects, including nausea, vomiting and diarrhoea. In this patient population, however, it is difficult to distinguish between adverse effects caused by itraconazole and those caused by concomitant medication.[52]

3.3.3 Chemotherapy Recipients

Patients receiving chemotherapy are also in need of a formulation of itraconazole with high bioavailability because of the adverse effects of the chemotherapy regimen, such as damage to the rapidly dividing cells of the oral and intestinal mucosa.[26] The bioavailability of itraconazole oral solution is not affected in patients receiving standard remission-induction therapy for acute myeloid leukaemia; the C_{min} was greater than 250 μg/L by day 8 with itraconazole oral solution 5 mg/kg/day.[53] Itraconazole plasma concentrations sufficient to prevent systemic fungal infections can also be achieved in neutropenic patients with haematological malignancies.[54]

Adverse events, including anaemia, gastrointestinal bleeding, diarrhoea, fever and vomiting have been experienced by patients receiving chemotherapy and itraconazole oral solution, but they are thought to be related to the underlying disease, the chemotherapy or bacteraemia rather than the study drug.[53]

3.3.4 Paediatric Patients

Fungal infections are a major problem in children, particularly those undergoing surgery[55] or receiving chemotherapy for leukaemia and other haematological malignancies.[56] The introduction of the azole antifungal agents for the treatment, prevention and empirical therapy of fungal infections has dramatically increased survival rates in children at high risk.[57]

Itraconazole oral solution is more suited to paediatric use than capsules because children may have difficulty in swallowing, even without the

additional complication of mucositis. Furthermore, adjusting the dosages of capsules for children can prove troublesome.[58] The pharmacokinetics of antifungal agents cannot be assumed to be similar in adults and children, as shown by the shorter $t_{1/2}$ of fluconazole in children than in adults.[59] In immunocompromised children, itraconazole oral solution 5 mg/kg/day produces a C_{max} of 631 μg/L and an AUC_{24h} of 8770 μg/L/hour after 14 days, which are lower values than those in healthy or immunocompromised adults.[58] Other pharmacokinetic parameters, including $t_{1/2}$, are similar in children and adults receiving itraconazole oral solution. Young children, aged from 6 months to 5 years, may have lower plasma concentrations of itraconazole after administration of the oral solution (mean C_{max} ranging from 534 μg/L to 571 μg/L), although these are still within the therapeutic range. Bearing in mind these pharmacokinetic differences, an increase in the dose of itraconazole according to bodyweight may be justified for children under the age of 12 years.[58]

The tolerability of itraconazole oral solution in children is generally good, with transient gastrointestinal symptoms observed most frequently. In a trial of itraconazole oral solution in infants and children at risk of developing systemic fungal infections, no consistent, clinically relevant changes in laboratory data were seen, apart from a borderline increase in ALT in one patient with acute lymphoblastic leukaemia.[58]

4. IV Formulation

The IV formulation of itraconazole is also formed from a complex of itraconazole and cyclodextrin.

4.1 Bioavailability

For the IV formulation, an alternative dosage schedule has been designed that allows steady-state plasma concentrations to be achieved more rapidly than with the oral solution. A 1-hour IV infusion of itraconazole 200mg twice daily for 2 days is sufficient to achieve an itraconazole concentration that exceeds a plasma concentration (C_{min}) of 250 to 500 μg/L in healthy volunteers. Once-daily administration at the same dose from day 3 onwards maintains the plasma concentration at the same steady-state level.[60] In patients with invasive pulmonary aspergillosis, 91% of the population achieved these plasma concentrations after 2 days of itraconazole IV administration (200mg twice daily).[61]

4.2 Elimination

After IV administration of itraconazole, cyclodextrin is rapidly eliminated by glomerular filtration, with little accumulation in the body.[25] Patients with impaired renal function or those receiving dialysis, therefore, may not be ideal candidates for high doses of IV itraconazole, although clinical evidence to support this is lacking.

4.3 Pharmacokinetics of Itraconazole IV in Different Patient Groups

In patients at high risk, such as those requiring intensive care, oral administration may be problematical. The IV preparation of itraconazole is the optimal treatment in such patients. The different formulations of itraconazole can be used sequentially for the treatment of fungal infections. Generally, this involves the use of an initial course of IV itraconazole to attain high plasma concentrations rapidly, followed by a maintenance course of itraconazole oral solution or capsules. During IV treatment, steady-state concentrations of itraconazole are reached within 48 hours in patients in intensive care units (ICUs)[62] and patients with haematological malignancy[63] and within 60 hours in patients with advanced HIV infection.[25]

4.3.1 Patients with HIV Infection

A pharmacokinetic study of IV itraconazole (200mg infusion twice daily for 2 days then 200mg once daily for 5 days) followed by capsules (200mg twice daily or 200mg once daily, for 28 days) in patients with advanced HIV infection showed that this regimen is well tolerated and can provide effective treatment for a wide range of systemic fungal infections.[25] Few adverse events

are associated specifically with the IV formulation and most are related to the administration of the drug, such as injection-site reactions and vein disorders, which occur with many IV treatments. In clinical trials, about 5% of patients reported mild nausea, diarrhoea, abdominal pain, headache and rash during the IV phase of treatment.[25]

4.3.2 Patients in Intensive Care

In an ICU trial, patients received 4 infusions of IV itraconazole 200mg over the first 2 days, followed by IV itraconazole 200 mg/day for 5 days and then itraconazole oral solution 200mg once or twice daily for 2 weeks. Target plasma concentrations in excess of 250 μg/L were reached after the first 2 days of IV treatment and were maintained throughout the IV treatment period. Twice-daily administration of the oral solution (400 mg/day) for 2 weeks preserved, or in some cases increased, the itraconazole plasma concentrations, whereas once-daily follow-up (200 mg/day) led to suboptimal plasma concentrations of itraconazole.[62] Gastrointestinal adverse events were reported by some patients, but other adverse events were considered to be symptoms of the underlying disease in this critically ill patient population, rather than related to the administration of itraconazole.[62]

4.3.3 Patients with Haematological Malignancy

A study of 7 days of IV itraconazole followed by 2 weeks of itraconazole oral solution in patients with haematological malignancy showed that this regimen was effective and well tolerated. Patients received four 1-hour infusions of 200mg itraconazole during the first 2 days and then a 1-hour infusion of itraconazole 200mg once daily for the next 5 days. During the IV treatment phase, steady-state plasma concentrations of itraconazole and hydroxy-itraconazole were reached within 48 and 96 hours, respectively. Patients then received itraconazole oral solution for 2 weeks, either 200mg twice daily or 200mg once daily. As with the ICU trial, only twice-daily administration of the oral solution (400 mg/day) maintained or increased the itraconazole plasma concentrations obtained at the end of the IV treatment phase.[63] Adverse events were reported by most patients but, apart from gastrointestinal disorders, all were considered to be unrelated to the study drug.[63]

5. Conclusion

Itraconazole, in all its formulations, is a well tolerated antifungal agent with a proven track record in treating many types of fungal infections successfully. Itraconazole capsules, which have been available for many years, provide excellent results in patients with superficial and subcutaneous fungal infections, but may have variable bioavailability in immunocompromised patients with mucosal damage. The two new formulations of itraconazole – oral solution and IV – are well tolerated and the addition of cyclodextrin does not significantly negatively affect the adverse event profile. The enhanced bioavailability of the oral solution and IV forms ensures that they reliably achieve target plasma concentrations, especially in patients at high risk. The enhanced flexibility provided by multiple formulations of this effective antifungal agent allows adaptation of the itraconazole treatment regimen according to an individual patient's needs.

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