Itraconazole

Brand Name: Sporanox
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Itraconazole, a synthetic triazole derivative, is an azole antifungal agent. [1]

HIV/AIDS-Related Uses

Itraconazole was approved by the FDA on September 11, 1992, for use in the treatment of adults coinfected with Penicillium marneffei and HIV. It is also approved for use as an alternative agent for the treatment or suppressive maintenance of cryptococcal meningitis in patients with AIDS and other immunocompromised conditions.[2] Itraconazole is also used orally for the prevention of serious fungal infections (e.g., coccidiodomycosis, cryptococcosis, histoplasmosis, mucocutaneous candidiasis) in patients with HIV infection.[3]

Non-HIV/AIDS-Related Uses

Itraconazole is indicated in the treatment of aspergillosis (especially in patients who are intolerant of or refractory to amphotericin B therapy); blastomycosis; oropharyngeal, chronic mucocutaneous, and vulvovaginal candidiasis; chromomycosis; coccidiodomycosis; histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; cryptococcal meningitis; onychomycosis; paracoccidiodomycosis; tinea corporis, tinea cruris, tinea pedis, and tinea manuum; extrameningeal cryptococcosis; cutaneous leishmaniasis; febrile neutropenia; fungal paronychia; Penicillium marneffei infection; fungal pneumonia; fungal septicemia; and disseminated sporotrichosis.[4]

Pharmacology

Itraconazole is fungistatic and may be fungicidal, depending on the concentration. Azole antifungals interfere with cytochrome P450 (CYP) enzyme activity necessary for the demethylation of 14-alpha-methyl sterols to ergosterol, the principal sterol in fungal cell membranes. As ergosterol is depleted, the cell membrane is damaged. In Candida albicans, azole antifungals inhibit transformation of blastospores into the invasive mycelial form. Itraconazole, unlike ketoconazole, has a very weak, noncompetitive inhibitory effect on the CYP enzyme system while maintaining a high affinity for fungal CYP enzyme activity. It reportedly does not have antiandrogenic activity and does not affect cortisol metabolism at clinically recommended doses.[5]

Gastrointestinal (GI) absorption of itraconazole is affected by achlorhydria or hypochlorhydria (no or low acid levels in the stomach); because cases of HIV infected individuals with these conditions have been reported, physicians should consider this in their decision to use itraconazole.[6] Bioavailability of itraconazole when given in capsule form is 40% to 55% in the fasting state and 90% to 100% when taken with food. The bioavailability of the oral solution form is 90% to 100% in the fasting state and 55% when taken with food. The time to peak serum concentration may be from 2.5 hours to 4.4 hours, depending on formulation and whether the drug was taken with food.[7]

Itraconazole is highly lipophilic and is extensively distributed to tissues, concentrating in fatty tissues, omentum (lining of the bowel wall), liver, and kidneys. Aqueous fluids, such as the cerebrospinal fluid, aqueous humor, and saliva, contain negligible concentrations of itraconazole. Itraconazole does not distribute into peritoneal dialysate effluent. Exudates such as pus may have up to 3.5 times the simultaneous plasma concentration of the drug, while tissues that are prone to fungal invasion, such as the skin, lung tissue, and the female genital tract, have several times the plasma concentration.[8]

Itraconazole is in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. Based on the teratogenic and embyrotoxic effects shown in animal studies, itraconazole should only be used during pregnancy or nursing when the potential benefits justify the possible risks to the fetus or nursing infant. Animal studies indicate that itraconazole causes a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity. In rats, these consist of major skeletal defects at doses

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Pharmacology (cont.)

approximately 5 to 20 times the maximum recommended human dose (MRHD); in mice, these consist of encephaloceles and/or macroglossia at doses 10 times the MRHD. Itraconazole did not affect the fertility of male or female rats treated with oral doses of up to 5 times the MRHD, although parental toxicity was present at this dosage level. Itraconazole is distributed into breast milk.[9]

Itraconazole binding to proteins is very high (99%). Metabolism of itraconazole is primarily hepatic. Biliary excretion of the capsule form is estimated to be 3% to 18%.[10] Adjustment of oral itraconazole dosage in patients with renal impairment appears unnecessary; itraconazole injection should not be given to patients with creatinine clearance less than 30 ml/min, because severe renal impairment reduces clearance of hydroxypropyl beta-cyclodextrin (an excipient contained in itraconazole injection). While the effect of hepatic impairment on itraconazole pharmacokinetics currently remains unclear, plasma concentrations of the drug should be monitored carefully in patients with such impairment.[11]

Itraconazole capsules and oral solution should not be used interchangeably. Drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. In addition, the topical effects of mucosal exposure may be different between the two formulations.[12]

Adverse Events/Toxicity

Adverse effects seen with azole antifungals include hypersensitivity; agranulocytosis; exfoliative skin disorders, including Stevens-Johnson syndrome; hepatotoxicity; thrombocytopenia; central nervous system effects; and GI disturbances.[13]

The most common adverse events to itraconazole injection in pharmacologic testing have been nausea, hypokalemia, bilirubinemia, diarrhea, and vomiting. The injection is associated with increased levels of hepatic enzymes, abnormal hepatic function, and jaundice, which may be indicative of possible liver disease. If patients develop clinical signs and symptoms consistent with liver disease, the administration of IV itraconazole should be discontinued. The oral solution is safe and generally well tolerated; the most common adverse effects are nausea, diarrhea, and fever.[14] The most common side effects seen with itraconazole capsule use in the treatment of systemic fungal infections have been nausea and skin rash.[15]

Drug and Food Interactions

In addition to those drugs contraindicated with its use, many drugs may produce interactions if administered concurrently with itraconazole. Antacids, anticholinergics, antispasmodics, histamine-2 receptor antagonists, omeprazole, and sucralfate may increase GI pH, thus reducing absorption of itraconazole. Patients should be advised to take these medications at least 2 hours after taking itraconazole. Itraconazole should be taken at least 2 hours before or 2 hours after buffered didanosine is taken.[16] Patients with achlorhydria or hypochlorhydria (no or low acid levels in the stomach) will have decreased absorption of itraconazole. Itraconazole capsules should be taken with a full meal to ensure maximal absorption of the medication; itraconazole oral solution should be taken on an empty stomach to increase absorption of the medication.[17]

Concurrent use of itraconazole with oral antidiabetic agents such as tolbutamide, chlorpropamide, glyburide, or glipizide has increased the plasma concentrations of these sulfonylurea agents, leading to hypoglycemia; blood glucose concentrations should be monitored, as the dose of oral hypoglycemic agent may need to be reduced. Itraconazole may inhibit the metabolism of the antineoplastics busulfan, docetaxel, and vinca alkaloids. Use of itraconazole with calcium channel blockers (e.g., felodipine, nifedipine, verapamil) may result in edema; dosage adjustment may be needed. Caution should be used as itraconazole may inhibit calcium channel blockers' metabolism and these drugs can have a negative inotropic effect that may be additive to those of itraconazole.[18] Concurrent use of itraconazole with benzodiazepines (e.g., alprazolam, diazepam, midazolam, triazolam) elevates the plasma concentration of the benzodiazepines, which may potentiate and prolong

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Drug and Food Interactions (cont.)

their hypnotic and sedative effects.[19]

Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin) may decrease itraconazole plasma concentrations, leading to treatment failure or clinical relapse. Use of immunosuppressive drugs such as cyclosporine, methylprednisolone, sirolimus, or tacrolimus with itraconazole should be monitored carefully because itraconazole may inhibit their metabolism, increasing the plasma concentration of these drugs to toxic levels. Itraconazole may increase serum digoxin or alfentanil concentrations, leading to toxicity. Rifampin and rifabutin may increase the metabolism of itraconazole and other azoles, thus lowering the plasma concentration, which may lead to clinical failure or relapse. Macrolide antibiotics (e.g., clarithromycin, erythromycin) are known inhibitors of CYP3A4 and may increase plasma concentrations of itraconazole.[20] The anticoagulant effects of warfarin may be increased when warfarin is used concurrently with any azole antifungal, resulting in an increase of prothrombin time; patients on a concurrent regimen should be monitored carefully.[21]

Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes, such as amphotericin B. Itraconazole may increase plasma concentrations of protease inhibitors (e.g., indinavir, ritonavir, saquinavir); conversely, indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Nevirapine (and potentially other nucleoside reverse transcriptase inhibitors) may induce the metabolism of itraconazole and has been shown to reduce the bioavailability of ketoconazole, another azole antifungal.[22]

People allergic to fluconazole or ketoconazole may also be allergic to itraconazole, another antifungal in this drug family.[23]

Contraindications

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or with a history of CHF. If signs or symptoms of CHF occur during administration of itraconazole capsules, the drug should be discontinued.[24] Negative inotropic effects were seen when itraconazole was administered intravenously to healthy human volunteers. If signs or symptoms of CHF occur during the administration of itraconazole injection, continued itraconazole use should be reassessed.[25]

Coadministration of cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol (lemomethadyl) with itraconazole capsules, injection, or oral solution is contraindicated. Itraconazole, a potent cytochrome CYP3A4 inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, or sudden death, have occurred in patients using cisapride, pimozide, levomethadyl, or quinidine concomitantly with itraconazole or other CYP3A4 inhibitors.[26]

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition, and some of these cases developed within the first week of treatment. If clinical signs or symptoms consistent with liver disease develop, treatment should be discontinued and liver function testing performed. Continued itraconazole use or reinstitution of treatment is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk.[27]

Itraconazole is contraindicated in patients who have shown hypersensitivity to itraconazole and should be prescribed with caution to patients with hypersensitivity to other azoles.[28] Concurrent use of itraconazole with astemizole, terfenadine, atorvastatin, cerivastatin, lovastatin, or simvastatin is contraindicated.[29]

Clinical Trials

For information on clinical trials that involve Itraconazole, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Itraconazole AND HIV Infections.

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Dosing Information

Mode of Delivery: Oral, intravenous.[30]

Dosage Form: Capsules containing itraconazole 100 mg.[31]

Oral solution containing itraconazole 10 mg/ml.[32]

Injection for intravenous infusion in one 25 ml colorless glass ampule containing itraconazole 10 mg/ml in pyrogen-free solution.[33]

Storage: Store capsules at a controlled room temperature of 15 C to 25 C (59 F to 77 F) and protect from light and moisture.[34]

Store oral solution at or below 25 C (77 F) and protect from freezing.[35]

Store injection at or below 25 C (77 F) and protect from light and freezing.[36]

Chemistry

CAS Name: 3H-1,2,4-Triazol-3-one, 4-(4-(4-(4-((2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-1-piperazinyl)phenyl)-2,4-dihydro-2-(1-methylpropyl)-[37]

CAS Number: 84625-61-6[38]

Molecular formula: C35-H38-Cl2-N8-O4[39]

C59.57%, H5.43%, Cl10.05%, N15.88%, O9.07%[40]

Molecular weight: 705.65[41]

Melting point: 166.2 C[42]

Physical Description: White to slightly yellowish powder.[43]

Stability: After reconstitution with 0.9% sodium chloride for injection, itraconazole injection may be stored refrigerated (2 C to 8 C) or at room temperature (15 C to 25 C) for up to 48 hours when protected from direct light. During administration, exposure to normal room light is acceptable.

Itraconazole injection should not be diluted with 5% dextrose in water for injection or with lactated Ringer's solution alone or in combination with any other diluent. The compatibility of itraconazole with diluents other than 0.9% sodium chloride for injection is not known.[44]

A dedicated infusion line should be used for administration of itraconazole injection; do not introduce concomitant medication in the same bag or same line as itraconazole injection.[45]

Correct preparation and administration of itraconazole injection are necessary to ensure maximal efficacy and safety. A precise mixing ratio is required in order to obtain a stable admixture. It is critical to maintain a 3.33 mg/ml itraconazole:diluent ratio. Failure to maintain this concentration will lead to the formation of a precipitate.[46]

Solubility: Lipophilic; practically insoluble in water and diluted acidic solutions.[47] Very slightly soluble in alcohols and freely soluble in dichloromethane, and it has a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.[48]

Other Names

Itraconazol[49]

Further Reading

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Manufacturer Information

Itraconazole
Janssen Pharmaceutica Inc
1125 Trenton-Harbourton Rd / PO Box 200
Titusville, NJ 08560-0200
(800) 526-7736

Sporanox
Ortho Biotech
P.O. Box 6914
430 Rt. 22 East
Bridgewater, NJ 08807-0914
(800) 682-6532

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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