Fluconazole

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

Drug Description

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

HIV/AIDS-Related Uses

Oral or intravenous (IV) fluconazole is used in the treatment of oropharyngeal, esophageal, and vulvovaginal candidiasis in immunocompromised adults with AIDS, advanced AIDS-related complex, malignancy, or other serious underlying disease. Fluconazole appears to be at least as effective, and in some cases more effective, than other antifungal agents used in the initial treatment of these candidal infections and is considered a drug of choice. HIV infected patients with severe or recurrent episodes of these types of candidiasis may benefit from long-term suppressive or maintenance therapy with fluconazole to prevent relapse.[2] Fluconazole may also be used for primary prophylaxis and for long-term suppressive or chronic maintenance therapy to prevent recurrence or relapse of serious fungal infections in patients considered at high risk for developing such infections, such as those with AIDS. These infections include coccidioidomycosis, cryptococcosis, histoplasmosis, and mucocutaneous candidiasis.[3]

Fluconazole is also indicated for the treatment and suppression of cryptococcal meningitis as a less toxic (albeit less efficacious) course of treatment than amphotericin B with flucytosine in AIDS patients. Although amphotericin B (with or without flucytosine) has been considered the initial treatment of choice for cryptococcal meningitis, fluconazole is an alternative for these infections in patients whose disease is not severe, because it is well tolerated and is distributed into cerebrospinal fluid at high concentrations. In maintenance therapy, fluconazole is usually better tolerated than amphotericin B alone.[4]

Non-HIV/AIDS-Related Uses

Fluconazole is indicated in the prophylaxis and treatment of esophageal, oropharyngeal, disseminated, chronic mucocutaneous, and vulvovaginal candidiasis; coccidiodomycosis; cryptococcal meningitis; onychomycosis; febrile neutropenia; fungal pneumonia; fungal septicemia; tinea corporis, tinea cruris, tinea pedis, and tinea manuum.[5]

Fluconazole is approved by the FDA for the treatment of systemic candidal infections and is an appropriate, less toxic alternative to amphotericin B.[6]

Pharmacology

Fluconazole is fungistatic and may be fungicidal, depending on the concentration. Azole antifungals interfere with fungal cytochrome P450 enzyme activity necessary for the demethylation of 14-alpha-methylsterols to ergosterol, the principal sterol in fungal cell membranes. As ergosterol is depleted, the fungal cell membrane is damaged. Unlike ketoconazole, fluconazole has a very weak, noncompetitive inhibitory effect on the liver CYP enzyme system but maintains a high affinity for fungal CYP enzyme activity. In Candida albicans, azole antifungals inhibit transformation of blastospores into invasive mycelial form. Fluconazole has not been reported to have antiandrogenic activity at currently used doses, and it does not affect cortisol metabolism in patients treated with clinically recommended doses.[7]

Fluconazole is rapidly and almost completely absorbed from the gastrointestinal (GI) tract. Oral bioavailability of fluconazole exceeds 90% in healthy, fasting adults; peak plasma concentrations of the drug are generally attained within 1 to 2 hours after oral administration. Limited studies indicated that bioavailability for adults with HIV appears similar to that seen in healthy adults. Unlike other antifungal agents (e.g., itraconazole, ketoconazole), GI absorption of fluconazole does not appear to be affected by gastric pH.[8]

Following oral or IV administration, fluconazole is widely distributed throughout the body, with good penetration of cerebrospinal fluid (ranging from 50% to 94% of concurrent plasma concentrations in patients with fungal meningitis), the eye, and peritoneal fluid. The apparent volume of

Fluconazole

Pharmacology (cont.)

distribution of fluconazole approximates that of total body water and has been reported to be 0.7 l/kg to 1 l/kg. It is not known if fluconazole crosses the placenta, but fluconazole is distributed into human milk in concentrations similar to those attained in plasma.[9]

Fluconazole is in FDA Pregnancy C. Fluconazole was administered orally to pregnant rabbits during organogenesis in 2 studies, at 5, 10, and 20 mg/kg, and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (20 to 60 times the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs or renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20 to 60 times the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis, and parturition.[10]

There are no adequate and well-controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 to 800 mg/day) fluconazole therapy for coccidioidomycosis (an off-label use). The relationship between fluconazole use and these events is unclear. Fluconazole should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.[11]

Unlike itraconazole and ketoconazole, fluconazole exhibits very low binding to proteins (11% to 12%). Metabolism of fluconazole is primarily hepatic. The plasma elimination half-life of fluconazole in healthy adults is approximately 30 hours (ranging from 20 hours to 50 hours). In patients with impaired renal function, plasma concentrations of fluconazole are higher and the half-life is prolonged; elimination half-life of the drug is inversely proportional to the patient's creatinine clearance.[12] [13]

Fluconazole is largely excreted in urine, and fluconazole elimination is principally renal. Renal clearance of the drug averages 0.27 ml/min per kg in adults with normal renal function. Approximately 60% to 80% of a single oral or IV dose of fluconazole is excreted in urine unchanged, and about 11% is excreted in urine as metabolites. Small amounts of the drug are excreted in feces. Fluconazole is removed by hemodialysis and peritoneal dialysis. A 3-hour hemodialysis session decreases plasma levels by approximately 50%.[14] [15]

Resistance to fluconazole can be produced in vitro by serial passage of Candida albicans in the presence of increasing concentrations of the drug. Some Candida species (e.g., C. krusei) are intrinsically resistant to fluconazole, and many strains of C. glabrata are resistant to the drug. Prolonged or intermittent use of oral fluconazole in immunocompromised patients has been suggested as a major contributing factor to the emergence of fluconazole resistance in candidal infections. Fluconazole-resistant fungi may also be cross resistant to other azole antifungal agents (e.g., itraconazole, ketoconazole). Although the clinical importance is unclear, fluconazole-resistant strains of C. albicans that were cross resistant to amphotericin B have been isolated from a few immunocompromised individuals, including patients with leukemia and HIV.[16]

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.[17]

The most common adverse events to fluconazole in pharmacologic testing have been headache, nausea, and abdominal pain. Clinical adverse effects were reported more frequently in HIV infected patients

Adverse Events/Toxicity (cont.)

than in HIV uninfected patients.[18] With the use of fluconazole, there is an increased risk of agranulocytosis, thrombocytopenia, and exfoliative skin disorders, such as Stevens-Johnson syndrome.[19]

Drug and Food Interactions

The rate and extent of GI absorption of fluconazole is not affected by food.[20]

In addition to those drugs contraindicated with its use, many drugs may produce interactions if taken concurrently with fluconazole. Concurrent use of fluconazole with oral antidiabetic agents, such as tolbutamide, chlorpropamide, glyburide, or glipizide, has increased the plasma concentrations of these sulfonylurea agents. Hypoglycemia has been noted with these agents, and blood glucose concentrations should be monitored, as the dose of oral hypoglycemia agent may need to be reduced. 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 such a regimen should be monitored carefully. Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin) may decrease fluconazole plasma concentrations, leading to treatment failure or clinical relapse. Use of immunosuppressive drugs such as cyclosporine, methylprednisolone, sirolimus, and tacrolimus or the antiasthmatic theophylline with concurrent fluconazole should be monitored carefully because fluconazole may inhibit their metabolism, increasing the plasma concentration of these drugs to toxic levels. Use of fluconazole with astemizole and other drugs metabolized by the CYP450 system may be associated with elevations in serum levels of these drugs. Rifampin and rifabutin may increase the metabolism of fluconazole and other azoles, lowering the plasma concentration, which may lead to clinical failure or relapse.[21] [22]

Amphotericin B may have an antagonistic relationship with fluconazole, but it is unclear if such antagonism actually occurs in vivo. Flucytosine may have a synergistic, additive, or indifferent effect when used with fluconazole, possibly because fluconazole damages the fungal cell membrane, allowing greater intercellular penetration of flucytosine. Central nervous system toxicity has been reported when amitriptyline, a tricyclic antidepressant, is used concurrently with fluconazole; increased serum concentrations of amitriptyline have been observed and are presumably related to fluconazole interfering with amitriptyline metabolism. Concurrent use of thiazide diuretics with fluconazole may increase peak fluconazole plasma concentrations, presumably because the diuretic decreases renal clearance of fluconazole by as much as 20%.[23]

Concomitant administration of fluconazole with HIV protease inhibitors may have clinically important effects; use with indinavir may result in a decrease in serum concentrations of indinavir, whereas use with ritonavir may result in an increase in serum concentrations of ritonavir. Fluconazole may interfere with zidovudine metabolism and increase serum concentrations of this nucleoside reverse transcriptase inhibitor.[24]

Contraindications

Fluconazole is contraindicated for patients who have shown hypersensitivity to fluconazole and should be prescribed with caution to patients with hypersensitivity to other azoles. Coadministration of fluconazole with cisapride or terfenadine is contraindicated because of reports of cardiac events, including torsades de pointes and serious cardiac dysrhythmias.[25]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral, intravenous infusion.[26]

Dosage Form: Tablets containing fluconazole 50 mg, 100 mg, 150 mg, or 200 mg.[27]

Oral suspension containing fluconazole 10 mg/ml in 35-ml bottles.[28]

Fluconazole

Dosing Information (cont.)

Injection for IV infusion containing fluconazole 200 mg/100 ml (2 mg/ml) or 400 mg/200 ml (2 mg/ml) in 5.6% dextrose diluent in Viaflex Plus plastic containers.[29]

Injection for IV infusion containing fluconazole 200 mg/100 ml (2 mg/ml) or 400 mg/200 ml (2 mg/ml) in 0.9% sodium chloride in glass bottles or Viaflex Plus plastic containers.[30]

Storage: Store tablets and oral suspension below 30 C (86 F), preferably between 5 C to 30 C (41 F to 86 F), in a well-closed container. Protect reconstituted oral suspension from freezing and store between 5 C to 30 C (41 F to 86 F), with unused portions discarded after 2 weeks.[31]

Protect fluconazole injection in glass bottles from freezing and store between 5 C to 30 C (41 F to 86 F). Protect fluconazole injection in Viaflex Plus plastic containers from freezing and store between 5 C to 25 C (41 F to 77 F). Brief exposures to temperatures up to 40 C (104 F) will not adversely affect the product.[32] [33]

Chemistry

CAS Name: 1H-1,2,4-Triazole-1-ethanol, alpha-(2,4-difluorophenyl)-alpha-(1H-1,2,4-triazol-1-ylmethyl)-[34]

CAS Number: 86386-73-4[35]

Molecular formula: C13-H12-F2-N6-O[36]

C50.98%, H3.95%, F12.41%, N27.44%, O5.22%[37]

Molecular weight: 306.27[38]

Melting point: 138 C to 140 C[39]

Physical Description: White crystalline solid.[40]

Stability: Fluconazole injection has been used safely for up to 14 days of IV therapy. The oral suspension should be shaken well before using and should be stored between 5 C and 30 C (41 F to 86 F); unused portions should be discarded after 2 weeks.[41]

Solubility: Slightly soluble in water (aqueous solubility of 8 mg/ml at 37 C); 25 mg/ml at room temperature in alcohol.[42] Slightly soluble in saline.[43]

Other Names

UK-49858[44]

Fluconazol[45]

Further Reading

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Manufacturer Information

Fluconazole
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

Diflucan
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

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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