Fluconazole: A Review of Use in Children
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The azole antifungals have had a significant impact on the treatment of fungal diseases in the past decade. Fluconazole, ketoconazole, and itraconazole provide a wide spectrum of antifungal activity and are generally well tolerated.[1,2] With the increasing number of immunocompromised and critically ill patients who are at risk for disseminated fungal infections, these agents provide a useful alternative to amphotericin B.[3] This review will focus on the use of fluconazole in the pediatric population.

Mechanism and Spectrum of Activity
Fluconazole is a synthetic broad spectrum *bis*-triazole antifungal. Like the other azole antifungals, its fungistatic activity is the result of inhibition of lanosterol 14-alpha-demethylase, the fungal cytochrome P-450 enzyme responsible for converting lanosterol to ergosterol. By blocking ergosterol production, fluconazole alters the composition of fungal lipid membranes, resulting in changes in cellular function and an inability to reproduce.[1-3]

Like the other agents in this class, fluconazole has demonstrated *in vitro* and *in vivo* activity against *Cryptococcus neoformans* and many *Candida* species. *Candida krusei* and *C. glabrata*, however, are often resistant to fluconazole. It has also been shown to exhibit activity against *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*. Fluconazole demonstrates only limited activity against *Aspergillus flavus* and *A. fumigatus.*[1,2,4]

Current Indications
Fluconazole is currently approved by the FDA for use in adults with oral and esophageal candidiasis, candidal urinary tract infections, systemic candidal infections, vaginal candidiasis, and cryptococcal meningitis. It is also indicated for prophylaxis in adult patients following chemotherapy, radiation therapy, or bone marrow transplantation.[2]

Use in Children
Fluconazole has been studied in a variety of pediatric settings. As prophylactic therapy in immunocompromised children, fluconazole has an 80 to 90% efficacy rate. In children with documented fungal infections, fluconazole has demonstrated clinical success in 84 to 90% of patients treated, even in those with disease resistant to other antifungals.[1]

In one of the earliest papers documenting use in children, Viscoli and colleagues[5] described a pilot study of 34 episodes of candidiasis in 24 immunocompromised children, ages 13 days to 14 years. A single daily dose of 6 mg/kg was given orally or intravenously for all but two patients, who received 12 mg/kg for *C. parapsilosis* fungemia. Clinical cure or improvement was noted in 30 (88%) of the cases. In the four patients who failed to improve, amphotericin was used. One of those patients was known to have *C. krusei*, believed to be resistant to fluconazole.

Fluconazole has also been effective in the treatment of fungal septicemia in the neonatal population.[6,7] In a comparison study involving 24 infants, intravenous fluconazole at a dosage of 10 mg/kg for 1 day followed by 5 mg/kg/day was found to be as effective as amphotericin 1 mg/kg/day. Fluconazole was better tolerated and resulted in less need for additional placement of central intravenous catheters than amphotericin.[6]

Fluconazole has also been favorably compared to nystatin for the treatment of oropharyngeal candidiasis in immunocompromised children. In a multicenter trial involving 159 children, participants were randomly assigned to receive

either oral fluconazole (2-3 mg/kg/day) or nystatin (400,000 units four times daily) for a period of 14 days. Clinical cure was demonstrated in 91% of the patients treated with fluconazole, but only 51% of the patients given nystatin. Eradication of the organism was documented in 76% of the fluconazole patients and in 11% of the nystatin group.[8]

Other case reports of oral fluconazole use in children have included the treatment of candidal otitis media in immunocompromised children and as maintenance therapy in children with fungal arthritis or cryptococcal meningitis previously treated with amphotericin.[9,11]

Oral fluconazole has also recently been studied as a treatment for tinea capitis. Solomon and colleagues[12] studied 27 children who were treated with fluconazole at a dosage of either 1.5, 3, or 6 mg/kg/day for a period of 20 days. Cure rates were correlated to dosage, with an 89% cure rate for the 6 mg/kg/day dosage. All patients who responded remained disease-free at 6 week and 4 month follow-up.

Pharmacokinetics
Fluconazole is available in both oral and intravenous dosage forms. The bioavailability of the oral dosage forms is estimated to be greater than 90%. After oral administration, fluconazole serum concentrations peak within 1 to 2 hours. Fluconazole is widely distributed throughout the body, including the central nervous system. It is only 10-12% protein bound, with a volume of distribution of approximately 0.7 L/kg. The elimination half-life in adults is approximately 30 hours (usual range 20-50 hours). Steady state concentrations are achieved after 5 to 10 days of repeated treatment.[1,2]

The pharmacokinetics of fluconazole in pediatric populations have also been determined. In 1992, Lee and colleauges[13] studied 26 children with neoplastic diseases, ages 5 to 15 years, who were receiving fluconazole prophylaxis. Patients were given 2, 4, or 8 mg/kg/day for 7 days. At the end of treatment, the authors reported an average volume of distribution of 0.84 L/kg and a half-life of 18.1 hours.

Since that initial report, several other studies have been published. Seay and colleagues[14] conducted a prospective study of 10 immunocompromised children with leukemia or aplastic anemia, ages 1 to 15 years, receiving fluconazole. A single IV dose of 6 mg/kg was given, followed by seven oral 3 mg/kg doses.

The authors reported an oral bioavailability of 92%, with an average volume of distribution of 0.77 L/kg, clearance of 0.63 ml/min/kg, and an elimination half-life of 15.6 hours.

A slightly longer elimination half-life was reported by Nahata and Brady[15] in a study of nine children with HIV infection, ages 6 to 13 years, who received a single oral dose of either 2 or 8 mg/kg. In this trial, half-life ranged from 19.8 to 42.3 hours. A prolonged elimination has also been reported in adults with HIV infection. Further work needs to be done in this patient population.

The pharmacokinetic profile of fluconazole has also been studied in premature infants. Saxen and colleagues[16] evaluated 12 low-birth-weight infants given fluconazole 6 mg/kg every 72 hours for 5 doses. The authors found a mean volume of distribution of 1.18 L/kg after the first dose and 2.25 L/kg after the fifth. Half-life declined during treatment, from an average of 88.6 hours after the first dose to 55.2 hours at the end of the study. The authors concluded that dosing intervals may require adjustment after repeated doses in infants. Additional studies are needed to support a change in the standard dosage regimen.

Fluconazole is primarily cleared by renal excretion. In adults, greater than 80% of a dose appears in the urine unchanged.[1,2] In children, this number may be closer to 65%.[13] The remainder is metabolized. As a result of this reliance on renal function for elimination, fluconazole dosages must be adjusted in patients with significant renal dysfunction (see dosing information below).

Drug Interactions
Fluconazole, like other azole antifungals, can affect human as well as fungal cytochrome P450 enzyme function, resulting in numerous drug interactions. Compared with ketoconazole and itraconazole, fluconazole has much greater specificity for fungal cytochrome P450 and its use is less likely to result in significant drug interactions.[1,2,4]

Table 1. *Drugs which may have increased serum concentrations if given with fluconazole*
Caffeine
Cyclosporine
Phenytoin
Theophylline
Sulfonylureas
Warfarin
Zidovudine

Table 2. *Drugs which may decrease the serum concentration of fluconazole*
Carbamazepine
Hydrochlorothiazide
Isoniazid
Phenobarbital
Phenytoin
Rifabutin
Rifampin

In addition, fluconazole may increase the metabolite concentrations of terfenadine and astemizole. It is not clear whether this may result in significant toxicity. Administration of cimetidine with fluconazole may significantly increase serum fluconazole concentrations.

Fluconazole may also decrease the efficacy of oral contraceptives. Women receiving fluconazole should be cautioned **not to rely on oral contraceptives** as their sole means of birth control.[2]

Adverse Effects
In pre-marketing clinical trials, the most frequent adverse effects associated with fluconazole were nausea (in 3.7% of patients), headache (1.9%), skin rash (1.8%), vomiting (1.7%), abdominal pain (1.7%), and diarrhea (1.5%). Rare events occurring in less than 1% of patients included: seizures, alopecia, leukopenia, thrombocytopenia, transient elevations of cholesterol or triglyceride levels, and hypokalemia.[1,2,4]

Fluconazole has also been linked to several cases of severe hepatotoxicity, with two cases resulting in patient death. Many of these cases have involved severely ill, immunocompromised patients receiving multiple medications. At this time, there has been no correlation with gender, age, dose, or duration of treatment.[1-3]

Allergic reactions, including anaphylaxis, are rare, but have been reported. Severe dermatologic reactions have also been associated with fluconazole administration. All patients developing a rash during treatment should have therapy discontinued and be closely monitored for progression of the lesions.[1,2]

Teratogenic Risk
Congenital anomalies have been demonstrated following the administration of azole antifungals in both animal models and human case reports.[17,18] While single dose fluconazole therapy for vaginal candidiasis has not been linked with teratogenic effects, continued use of fluconazole has been associated with severe malformations. In an interesting case series, Pursley and coworkers presented three affected infants.[18] Two were born to the same mother receiving chronic fluconazole therapy after cryptococcal meningitis. In between these infants, the woman had stopped treatment with fluconazole and delivered two healthy infants.

Malformations associated with fluconazole in these cases include craniofacial anomalies such as brachycephaly, skull hypoplasia, craniosynostosis, abnormal thinning and bowing of the long bones, and cardiac defects such as ventricular septal defects.[17,18] All women of child bearing age who are receiving maintenance therapy with fluconazole should be informed of the risk for teratogenic effects and counseled regarding available methods of contraception.

Dosing Recommendations
Fluconazole is currently available as Diflucan® by Roerig in 50, 100, 150, and 200 mg tablets, 10 mg/ml and 40 mg/ml suspension formulations, and a 2 mg/ml injection.[2]

Based on the available data in pediatric populations, the recommended dosage regimen for children is 3 to 12 mg/kg/day administered once daily. Due to a prolonged elimination, premature neonates should receive a dosage of 3 to 12 mg/kg administered once every 72 hours.

Specific dosage regimens have been developed for several indications. For treatment of oral or esophageal candidiasis, a dosage of 6 mg/kg on the first day followed by 3 mg/kg daily should be given for 2 weeks. For patients with systemic candidal infections, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg given once daily.
For children with cryptococcal meningitis, a dosage of 12 mg/kg given once daily should be used, with treatment lasting up to 12 weeks after documentation of negative CSF cultures. For suppression of relapse of cryptococcal meningitis, a dosage of 6 mg/kg given once daily is suggested.

Dosages should be reduced in infants or children with significant renal dysfunction. In patients with an estimated creatinine clearance of 10 to 50 ml/min, a standard initial dose may be given, but subsequent doses should be reduced by 50%. Patients receiving hemodialysis should be given one dose after each dialysis.[2]

In summary, fluconazole has been used in a variety of pediatric and neonatal populations and appears to be both safe and effective for most patients. More research is needed, particularly on the effects of long-term fluconazole therapy in growing children.

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Pharmacology Literature Review

Fatal hyperphosphatemia after overdose

The author describes a case of hyperphosphatemia in a premature infant which resulted from oral administration of an overdose of sodium phosphate. The patient, a former 28 week gestation, 62 day old female, received 11 mmol of sodium phosphate rather than the appropriate dose of 11 mg (1 mmol = 31 mg). The infant had repeated seizures and developed an arrhythmia. Attempts at resuscitation were unsuccessful. This case illustrates the sensitivity of infants to electrolyte imbalance and highlights the need for accurate dosage calculations. Perlman JM. Fatal hyperphosphatemia after oral phosphate overdose in a premature infant. **Am J Health-Syst Pharm 1997;54:2488-90.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/5/97:

1. Zafirlukast (Accolate [®]), a leukotriene receptor antagonist, was added to the formulary for the treatment of asthma. The usual dosage in adults and children > 12 years of age is 20 mg (1 tablet) twice daily. This product is restricted to use by the Allergy/Immunology and Pulmonary divisions.
2. Mibefradil (Posicor[®]) and Quetiapine (Seroquel[®]) were rejected.