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FLUCONAZOLE: A REVIEW

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Abstract:
Fluconazole is a bis-triazole antifungal drug with novel pharmacokinetic properties (metabolic stability, relatively high water solubility) which contribute to its therapeutic activity. Fluconazole is a medication that is given either by mouth or intravenously. It is used to treat a variety of fungal infections, especially Candida infections of the vagina (yeast infections), mouth, throat, and bloodstream. This article describes about the uses of fluconazole drug in immunocompromised patients and in the treatment of other fungal infections. Fungal resistance to drugs in the azole class tends to occur gradually over the course of prolonged drug therapy, resulting in clinical failure in immunocompromised patients. It is also used to prevent infections in people with neutropenia due to cancer chemotherapy, transplant patients, and premature babies.
Fluconazole's spectrum of activity includes most Candida species (but not Candida krusei or Candida glabrata), Cryptococcus neoformans, some dimorphic fungi, and dermatophytes, among others. Fluconazole is a first-generation triazole antifungal medication.While the imidazole antifungals are mainly used topically, fluconazole and certain other triazole antifungals are preferred when systemic treatment is required because of their improved safety and predictable absorption when administered orally. Further study to evaluate higher dosages and to establish the efficacy of fluconazole relative to more established antifungal agents is required.
Keywords: *Fluconazole, Candidiasis, Mycoses, Immunocomprimised patients.*

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INTRODUCTION:

Fluconazole is a bis-triazole antifungal drug with novel pharmacokinetic properties (metabolic stability, relatively high water solubility) which contribute to its therapeutic activity [1].

Fluconazole is an antifungal medication that is given either by mouth or intravenously. It is used to treat a variety of fungal infections, especially Candida infections of the vagina (yeast infections), mouth, throat, and bloodstream.

It is also used to prevent infections in people with weak immune systems, including those with neutropenia due to cancer chemotherapy, transplant patients, and premature babies.

HISTORY:

Fluconazole was developed by scientists at Pfizer and was first marketed in 1990. It is now available as an inexpensive generic drug. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.

MECHANISM OF ACTION:

Like other imidazole- and triazole-class antifungals, fluconazole inhibits the fungal cytochrome P450 enzyme 14α-demethylase. Mammalian demethylase activity is much less sensitive to fluconazole than fungal demethylase. This inhibition prevents the conversion of lanosterol to ergosterol, an essential component of the fungal cytoplasmic membrane, and subsequent accumulation of 14α-methyl sterols [2]. Fluconazole is primarily fungistatic; however, it may be fungicidal against certain organisms in a dose-dependent manner, specifically Cryptococcus [3].

Pharmacodynamics

The antifungal activity of azole derivatives relates to their inhibition of membrane sterol synthesis by fungal cytochrome P450 enzymes. While ketoconazole also inhibits mammalian cytochrome P450 enzymes, supratherapeutic concentrations of fluconazole have a minimal effect on mammalian enzymes and, thus, fluconazole appears to be free of adverse effects on steroid hormone production.

Pharmacokinetics

Fluconazole is very well absorbed after oral administration even in the presence of food, or antacid or H2-receptor antagonist pretreatment, and its bioavailability exceeds 90%. The peak plasma concentrations achieved after single oral doses of fluconazole 100mg and 400mg are 1.9 mg/L and 6.7 mg/L, respectively, in healthy volunteers. Continued oral administration of fluconazole for 6 to 10 days leads to an increase in peak plasma concentration of 2.5 times that achieved after a single dose.

Fluconazole is widely distributed and its apparent volume of distribution (0.8 L/kg) approximates that of total body water. Concentrations in cerebrospinal fluid, saliva, sputum and vaginal fluid approximate those attained in the plasma. In contrast to other azole antifungals which are highly bound, fluconazole is only 11% protein bound.

The primary route of elimination is via renal excretion with up to 80% of the drug recovered in urine unchanged. The elimination half-life is approximately 30 hours and is prolonged in patients with decreased renal function, necessitating dosage modification. Fluconazole is removed by haemo- and peritoneal dialysis [4].

Medicinal Uses

Fluconazole is a first-generation triazole antifungal medication. It differs from earlier azole antifungals (such as ketoconazole) in that its structure contains a triazole ring instead of an imidazole ring. While the imidazole antifungals are mainly used topically, fluconazole and certain other triazole antifungals are preferred when systemic treatment is required because of their improved safety and predictable absorption when administered orally.

Fluconazole's spectrum of activity includes most Candida species (but not Candida krusei or Candida glabrata), Cryptococcus neoformans, some dimorphic fungi, and dermatophytes, among others.

Common uses include:

The treatment of non-systemic Candida infections of the vagina ("yeast infections"), throat, and mouth.

Certain systemic Candida infections in people with healthy immune systems, including infections of the bloodstream, kidney, or joints. Other antifungals are usually preferred when the infection is in the heart or central nervous system, and for the treatment of active infections in people with weak immune systems.

The prevention of Candida infections in people with weak immune systems, such as neutropenic due to cancer chemotherapy, those with advanced HIV infections, transplant patients, and premature infants.

As a second-line agent for the treatment of cryptococcal meningoencephalitis, a fungal infection of the central nervous system.

Fluconazole is a promising treatment of cryptococcal meningitis. The rate of clinical resolution and eradication of Cryptococcus neoformans from cerebrospinal fluid has been similar between fluconazole and amphotericin B.

Fluconazole has been well tolerated to date but wider clinical experience is needed, especially with regard to the rare occurrence of hepatotoxicity and exfoliative skin reactions.

The promising clinical response of patients with various forms of candidiasis or cryptococcosis — together with convenient administration regimens

— recommends fluconazole as a useful addition to currently available systemic antifungal therapies, in particular for the treatment of mycoses in patients with AIDS

Fluconazole penetrates the cerebrospinal fluid well and is approved for primary and suppressive therapy of cryptococcal meningitis in AIDS patients [5].

Fluconazole seemed more effective than ketocon azole in the treatment of oral thrush among AIDS and ARC patients [6].

Amphotericin B used in combination with flucytosine has superior mycologie and clinical efficacy compared with fluconazole for the treatment of cryptococcal meningitis in patients with AIDS [7].

Prophylactic fluconazole prevents colonization and superficial infections by Candida species other than Candida krusei in patients undergoing chemotherapy for acute leukemia and is well tolerated [8].

Fluconazole prophylaxis prevents colonization and invasive intra-abdominal Candida infections in high-risk surgical patients [9].

The observed synergy between fluconazole and terbinafine is not surprising, because mechanistically, these two agents inhibit different steps of the same pathway, namely, the ergosterol biosynthesis pathway. Barrett-Bee and Ryder [10]. Provided evidence that the simultaneous accumulation of squalene (as a result of terbinafine action) and 14-methylsterols (as a result of azole action) occurs in cases of *Candida* treated with terbinafine plus an azole.

Our findings suggest that the use of fluconazole plus terbinafine provides a possible therapeutic option for the treatment of fluconazole-refractory candidiasis [11].

In nonneutropenic subjects, the combination of fluconazole plus AmB was not antagonistic compared with fluconazole alone, and the combination trended toward improved success and more-rapid clearance from the bloodstream [12].

Alterations in the target enzyme, including functional amino acid substitutions and overexpression of the gene that encodes the enzyme, were detected in 65 and 35% of the isolates, respectively. Overall, multiple mechanisms of resistance were combined in 75% of the isolates displaying high-level fluconazole resistance. These results may help in the development of new strategies to overcome the problem of resistance as well as new treatments for this condition [13].

Fluconazole Adverse Reactions / Fluconazole Side Effects:

Nausea, abdominal pain, vomiting, diarrhoea, flatulence; elevated liver function values; headache; rash, exfoliative dermatitis. Rarely, angioedema, anaphylactic reactions and thrombocytopenia.

Potentially Fatal: Hepatotoxicity; rarely anaphylaxis; Stevens-Johnson syndrome.

Precautions

Some azoles, including Fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During postmarketing surveillance, there have been rare cases of QT prolongation and torsade de pointes in patients taking Fluconazole. Most of these reports involved seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Special Precautions

Renal or hepatic impairment. May prolong QT interval. Pregnancy, lactation.

DOSAGE [14]

1. Superficial Mucosal Candidiasis

Adult: (Except genital candidiasis) usual dose: 50 mg daily may increase to 100 mg daily if needed. Recommended treatment duration: 7-14 days (oropharyngeal candidiasis, except in severely immunocompromised patients), 14 days (atrophic oral candidiasis associated with dentures), 14-30 days (other mucosal candidiasis including oesophagitis).

Child: >4 weeks: Loading dose: 6 mg/kg followed by 3 mg/kg daily.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min)-Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

2. Candidal balanitis

Adult: 150 mg as a single dose.

3. Vaginal candidiasis

Adult: 150 mg as a single dose.

4. Dermatophytosis

Adult: 50 mg daily for up to 6 weeks.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min)-Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

5. Pityriasis Versicolor

Adult: 50 mg daily for up to 6 wk.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min) -Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

6. Cutaneous Candidiasis

Adult: 50 mg daily for up to 6 weeks.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min)- Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

7. Systemic Candidiasis

Adult: Initially, 400 mg followed by 200-400 mg daily. Max: 800 mg daily in severe infections. Treatment duration is based on clinical and mycological response but is usually at least 6-8 wk in cryptococcal meningitis. May also be given via IV infusion. To prevent relapse after a primary course of treatment for acute cryptococcal meningitis in AIDS patients: 100-200 mg daily, may also be given via IV admin.

Child: >4 wk: 6-12 mg/kg daily; same doses may given every 72 hr in neonates up to 2 wk and every 48 hr in neonates 2-4 wk. Max: 400 mg daily.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min)-Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

8. Cryptococcal Infections

Adult: Initially, 400 mg followed by 200-400 mg daily. Max: 800 mg daily in severe infections. Treatment duration is based on clinical and mycological response but is usually at least 6-8 weeks in cryptococcal meningitis. May also be given via IV infusion. To prevent relapse after a primary course of treatment for acute cryptococcal meningitis in AIDS patients: 100-200 mg daily, may also be given via IV admin.

Child: >4 wk: 6-12 mg/kg daily; same doses may given every 72 hr in neonates up to 2 wk and every 48 hr in neonates 2-4 wk. Max: 400 mg daily.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min)- Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

9.Prophylaxis of fungal infections in immunocompromised patients

Adult: 50-400 mg daily. May also be given via IV infusion.

Child: 3-12 mg/kg daily; may also be given via IV infusion. For infants <2 wk, doses should be given every 72 hr; 2-4 wk, doses should be given every 48 hr. Max: 400 mg daily, or 12 mg/kg at recommended intervals in infants.

Renal impairment: Normal initial doses; adjust subsequent doses based on CrCl. Patients on dialysis: Single recommended dose after each session.

CrCl (ml/min)-Dosage Recommendation <50 and not receiving dialysis Maintenance dose: 50% of the recommended doses.

List of Contraindications

Fluconazole and Pregnancy

Caution when used during pregnancy.

Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.

Fluconazole and Lactation

Caution when used during lactation.

Fluconazole and Children

An open-label, randomized, controlled trial has shown fluconazole to be effective in children 6 mo to 13 years of age. Efficacy has not been established in infants younger than 6 months of age.

DRUG INTERACTIONS:

In making a therapeutic recommendation, the clinician must consider both the efficacy and safety of a drug. Many drugs are substrates or inhibitors of CYP3A4, and thus have the potential to interact with other drugs which are metabolized by CYP3A4, such as erythromycin and itraconazole. The resulting increased serum concentration of the drug can produce serious adverse events, and in some cases, may even be fatal. Patients with multiple risk factors for cardiovascular disease and elderly patients receiving polypharmacy are particulary susceptible to drug interactions. By understanding the role of the cytochrome P450 enzyme system in drug metabolism, clinicians should be able to predict and avoid clinically significant drug interactions.

Other Drug Interactions:

Rifampicin reduces fluconazole levels. Reduces theophylline clearance. Affects efficacy of oral contraceptives. May increase serum levels of alprazolam, triazolam, midazolam, and diazepam. May raise serum concentrations and efficacy of oral sulphonylureas, phenytoin, ciclosporin, calcium channel blockers, tacrolimus, HMG-CoA reductase inhibitors (except pravastain and fluvastatin), warfarin and other anticoagulants. May reduce metabolism of caffeine. Avoid concurrent use with clopidogrel.

Potentially Fatal: Increased risk of cardiac arrhythmias with astemizole, cisapiride or terfenadine [15].

FDA is now saying treatment with chronic, high doses of fluconazole during the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants [16].

CONCLUSION:

Fluconazole is a first-generation triazole antifungal medication. It differs from earlier azole antifungals (such as ketoconazole) in that its structure contains a triazole ring instead of an imidazole ring. While the imidazole antifungals are mainly used topically, fluconazole and certain other triazole antifungals are preferred when systemic treatment is required because of their improved safety and predictable absorption when administered orally. Fluconazole's spectrum of activity includes most Candida species, as most of the etiological agents of fungal infections are from candida sps. Fluconazole would be the better choice in those type of infections. . Further study to evaluate higher dosages and to establish the efficacy of fluconazole relative to more established antifungal agents is required.

REFERENCES:

1. Susan M. Grant, Stephen P. Clissold. A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Superficial and Systemic Mycoses.
2. Pfizer Australia Pty Ltd. Diflucan (Australian Approved Product Information). West Ryde (NSW): Pfizer Australia; 2004.
3.Longley, Nicky; Muzoora, Conrad; Taseera, Kabanda; Mwesigye, James; Rwebembera, Joselyne; Chakera, Ali; Wall, Emma; Andia, Irene; Jaffar, Shabbar; Harrison, Thomas S. (2008). "Dose Response Effect of High-Dose Fluconazole for HIV-Associated Cryptococcal Meningitis in Southwestern Uganda". Clinical Infectious Diseases. 47 (12): 1556–1561. doi:10.1086/593194. ISSN 10q58-4838. PMID 18990067.
4.Walsh TJ, Foulds G, Pizzo PA. Pharmacokinetics and tissue penetration of fluconazole in rabbits. Antimicrobial Agents and Chemotherapy 33: 467–469, 1989.
5. Wragg PF, Howell RA, Hardy P, Farrelly PJ, Martin MV. An open non-comparative trial of fluconazole a new systemically-administered antifungal. Abstract. Journal of Dental Research 65: 515, 1986.
6.S. De Wit a, H. Goossens b, D. Weerts a, N. Clumeck a comparision of fluconazole and ketokonazole for oropharyngeal candidiasis in Aids.
7.Robert A. Larsen, MD; Mary Ann E. Leal, MD; and Linda S. Chan, PhD. Fluconazole Compared with Amphotericin B plus Flucytosine for Cryptococcal Meningitis in AIDS: A Randomized Trial
8.Drew J. Winston, MD; Pranatharthi H. Chandrasekar, MD; Hillard M. Lazarus, MD; Jesse L. Goodman, MD; Jeffrey L. Silber, MD; Harold Horowitz, MD; Richard K. Shadduck, MD; Craig S. Rosenfeld, MD; Winston G. Ho, MD; Muhammed Z. Islam, PhD; and Donald N. Buell, MD Fluconazole Prophylaxis of Fungal Infections in Patients with Acute Leukemia: Results of a Randomized Placebo-Controlled, Double-Blind, Multicenter Trial.
9.Eggimann, Philippe MD; Francioli, Patrick MD; Bille, Jacques MD; Schneider, Remy MD; Wu, Mei-Miau DPH; Chapuis, Germain MD; Chiolero, Rene MD; Pannatier, Andre PharmD; Schilling, Julian MD; Geroulanos, Stefanos MD, FCCM; Glauser, Michel P. MD; Calandra, Thierry MD, PhD. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients.
10. Barrett-Bee K, Ryder N S. Biochemical aspects of ergosterol biosynthesis inhibition. In: Sutcliffe J A, Georgopapadakou N H, editors. Emerging targets for antibacterial and antifungal chemotherapy. New York, N.Y: Chapman and Hall; 1992. pp. 410–436
11. Mahmoud A. Ghannoum* and Boni ElewskiSuccessful Treatment of Fluconazole-Resistant Oropharyngeal Candidiasis by a Combination of Fluconazole and Terbinafine 1999 Nov; 6(6): 921–923.
12.A Randomized and Blinded Multicenter Trial of High-Dose Fluconazole plus Placebo versus Fluconazole plus Amphotericin B as Therapy for Candidemia and Its Consequences in Nonneutropenic Subjects. Clinical Infectious Diseases (2009) 48 (5): 503-535
13. Antimicrobial Agents and Chemotherapy doi: 10.1128/AAC.45.10.2676-2684 October2001
14. WWW.Rxlist.name.
15. "US Pharmacist". Retrieved 2015-01-28
16.http://www.drugs.com/fda/diflucan-fluconazole-safety-communication-long-term-during pregnancy-may-associated-birth-defects-13013.html.