Antifungal Drugs

I. OVERVIEW

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature. Some mycotic infections are superficial and some involve the skin (cutaneous mycoses extending into the epidermis), but fungi may also penetrate the skin, causing subcutaneous infections. The fungal infections that are most difficult to treat are the systemic mycoses, which are often life threatening. The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes.

II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

A. Amphotericin B

Amphotericin B is a naturally occurring polyene macrolide antibiotic produced by Streptomyces nodosus. In spite of its toxic potential, amphotericin B is the drug of choice for the treatment of life-threatening systemic mycoses.

1. Mechanism of action: Several amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.

2. Antifungal spectrum: Amphotericin B is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of Aspergillus. [Note: Amphotericin B is also used in the treatment of the protozoal infection leishmaniasis.]

3. Resistance: Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

4. Pharmacokinetics: Amphotericin B is administered by slow, intravenous (IV) infusion. The three amphotericin B lipid formulations marketed in the United States are AMPHOTEC, ABELCET, and AMBISOME. These liposomal preparations have the primary advantage of reduced renal and infusion toxicity. Amphotericin B is extensively bound to plasma proteins and is distributed throughout the body. To minimize
nephrotoxicity, alternatives including sodium loading with infusions of normal saline and the lipid-based amphotericin B products are used.

5. Adverse effects: Amphotericin B has a low therapeutic index. The total adult daily dose should not exceed 1.5 mg/kg. Small test doses may be administered to assess the degree of negative responses, such as anaphylaxis or convulsions. Other toxic manifestations include the following.

a. Fever and chills: These occur most commonly 1 to 3 hours after starting the IV administration, but they usually subside with repeated administration of the drug.

b. Renal impairment: Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Creatinine clearance can drop, and potassium and magnesium are lost.

c. Hypotension: A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation.

d. Anemia: Normochromic, normocytic anemia caused by a reversible suppression of erythrocyte production may occur.

e. Neurologic effects: Intrathecal administration can cause a variety of serious neurologic problems.

f. Thrombophlebitis: Adding heparin to the infusion can alleviate this problem.

B. Flucytosine

1. Mechanism of action: 5-FC enters fungal cells via a cytosinespecific permease, which is an enzyme not found in mammalian cells. 5-FC is then converted by a series of steps to 5-fluorodeoxyuridine 5’-monophosphate. This false nucleotide inhibits thymidylate synthase, thereby depriving the organism of thymidylic acid, an essential DNA component.

2. Antifungal spectrum: 5-FC is fungistatic. It is effective in combination with itraconazole for treating chromoblastomycosis and in combination with amphotericin B for treating candidiasis and cryptococcosis.

3. Resistance: Resistance due to decreased levels of any of the enzymes in the conversion of 5-FC to 5-fluorouracil (5-FU) and beyond.
4. Pharmacokinetics: 5-FC is well absorbed by the oral route. It distributes throughout the body water and penetrates well into the CSF. Excretion of both the parent drug and its metabolites is by glomerular filtration.

5. Adverse effects: 5-FC causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Caution must be exercised in patients undergoing radiation or chemotherapy with drugs that depress bone marrow. Reversible hepatic dysfunction with elevation of serum transaminases and alkaline phosphatase may occur. Gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, are common, and severe enterocolitis may also occur.

C. Ketoconazole

Ketoconazole was the first orally active azole available for the treatment of systemic mycoses.

1. Mechanism of action: Azoles are predominantly fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol, the principal sterol of fungal membranes. This inhibition disrupts membrane structure and function, which, in turn, inhibits fungal cell growth. The drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production.

2. Antifungal spectrum: Oral ketoconazole is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species. Itraconazole has largely replaced ketoconazole in the treatment of most mycoses because of its broader spectrum, greater potency, and fewer adverse effects.

Topical ketoconazole is used to treat tinea corporis, tinea cruris, and tinea pedis. Also, topical ketoconazole is used to treat tinea versicolor, cutaneous candidiasis caused by Candida species. It is also used topically in the treatment of seborrheic dermatitis and dandruff.

3. Resistance: Identified mechanisms of resistance include mutations in the C-14 α-demethylase gene, which cause decreased azole binding. Additionally, some strains of fungi have developed the ability to pump the azole out of the cell.
4. Pharmacokinetics: When ketoconazole is administered orally, it requires gastric acid for dissolution and is absorbed through the intestinal mucosa. Administering acidifying agents before taking the drug can improve absorption in patients with achlorhydria. Ketoconazole is extensively bound to plasma proteins. Extensive metabolism occurs in the liver, and excretion is primarily through the bile.

5. Adverse effects: In addition to allergies, dose-dependent gastrointestinal disturbances, including nausea, anorexia, and vomiting, are the most common adverse effects of ketoconazole treatment. Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by ketoconazole. Frank hepatitis occurs rarely, but requires immediate cessation of ketoconazole treatment.

6. Drug interactions and contraindications: By inhibiting CYP450, ketoconazole can potentiate the toxicities of drugs such as cyclosporine. Rifampin, an inducer of the CYP450 system, can shorten the duration of action of ketoconazole. Drugs that decrease gastric acidity, such as H2-receptor blockers, antacids, and proton-pump inhibitors, can decrease absorption of ketoconazole. Finally, ketoconazole is teratogenic in animals, and it should not be given during pregnancy.

D. Fluconazole

Fluconazole is a member of the triazole class of antifungal products. It is clinically important because of its lack of the endocrine side effects of ketoconazole and its excellent penetrability into the CSF of both normal and inflamed meninges. Fluconazole is employed prophylactically, with some success, for reducing fungal infections in recipients of bone marrow transplants. It inhibits the synthesis of fungal membrane ergosterol in the same manner as ketoconazole and is the drug of choice for Cryptococcus neoformans after therapy with amphotericin B, for most candidemias, and for coccidioidomycosis. Fluconazole is effective against most forms of mucocutaneous candidiasis. Fluconazole is administered orally or intravenously. For the treatment of vaginal candidiasis, the dose is 150 mg as a single oral dose. The adverse effects caused by fluconazole treatment are less of a problem than those with ketoconazole. However, it can inhibit the P450 cytochromes that metabolize other drugs. Nausea, vomiting, and rashes are a problem. There is a caution for patients with liver dysfunction. Fluconazole is teratogenic, as are other azoles, and should not be used in pregnancy.
E. Itraconazole

Itraconazole is an antifungal agent with a broad antifungal spectrum. Like fluconazole, it is a synthetic triazole and also lacks the endocrinologic side effects of ketoconazole. Its mechanism of action is the same as that of the other triazoles. Itraconazole is the drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Itraconazole is well absorbed orally, but it requires acid for dissolution. Food increases the bioavailability of some preparations. Adverse effects include nausea and vomiting, rash, hypokalemia, hypertension, edema, and headache. Itraconazole should be avoided in pregnancy. The capsules should not be taken by patients with evidence of ventricular dysfunction.

F. Voriconazole

Voriconazole, a triazole, has the advantage of being a broad-spectrum antifungal agent. It is available for both IV and oral administration and is approximately 96 percent bioavailable. Voriconazole is approved for the treatment of invasive aspergillosis and has replaced amphotericin B as the treatment of choice for this indication. Voriconazole is also approved for treatment of serious infections. Side effects are similar to those of the other azoles. High trough concentrations are associated with visual and auditory hallucinations.

G. Posaconazole

Posaconazole, a triazole, is a new oral, broad-spectrum antifungal agent with a chemical structure similar to that of itraconazole. It was approved in 2006 to prevent Candida and Aspergillus infections. Due to its spectrum of activity, posaconazole could possibly be used in the treatment of fungal infections caused by Mucor species and other zygomycetes. To date, amphotericin B formulations are the only other antifungal agents available for treatment of zygomycete infections. The most common side effects observed were gastrointestinal issues (nausea, vomiting, diarrhea, and abdominal pain) and headaches. Rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported. To be effective, posaconazole must be administered with a high fat meal.

H. Echinocandins
Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β(1,3)-D-glucan, leading to lysis and cell death. Caspofungin, micafungin, and anidulafungin are available for IV administration once daily.

1. Caspofungin: Caspofungin is the first approved member of the echinocandins class of antifungal drugs. Caspofungin has activity against Aspergillus and most Candida species, including those species resistant to azoles. Adverse effects include fever, rash, nausea, and phlebitis. Flushing occurs. The dose of caspofungin does not need to be adjusted in renal impairment but is warranted with moderate hepatic dysfunction. Caspofungin is a second-line antifungal for those who have failed or cannot tolerate amphotericin B or an azole.

2. Micafungin and anidulafungin: Micafungin and anidulafungin are the newer members of the echinocandins class of antifungal drugs. Micafungin and anidulafungin have similar efficacy against Candida species. The dose of micafungin and anidulafungin does not need to be adjusted in renal impairment or mild-to-moderate hepatic dysfunction. Also, they are not substrates for CYP450 enzymes and do not have any associated drug interactions.

III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, resulting in the blocking of the biosynthesis of ergosterol, an essential component of fungal cell membrane.

1. Terbinafine: Oral terbinafine is the drug of choice for treating dermatophytoses and, especially, onychomycoses (fungal infections of nails). It is better tolerated, requires shorter duration of therapy, and is more effective than either itraconazole or griseofulvin.

   a. Mechanism of action: Terbinafine inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol. This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell.

   b. Antifungal spectrum: The drug is primarily fungicidal. Topical terbinafine is active against Trichophyton. It may also be effective against Candida albicans, Epidermophyton floccosum. Topical terbinafine 1% cream and solution are used to treat tinea pedis, tinea
corporis, and tinea cruris. Therapy is prolonged (usually about 3 months) but considerably shorter than that with griseofulvin.

c. Pharmacokinetics: Terbinafine is available for oral and topical administration, although its bioavailability is only 40 percent due to first-pass metabolism. Absorption is not significantly enhanced by food. Terbinafine is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and fat. Terbinafine accumulates in breast milk and should not be given to nursing mothers. A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues.

d. Adverse effects: The most common adverse effects from terbinafine are gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash. Taste and visual disturbances have been reported. Rarely, terbinafine may cause hepatotoxicity and neutropenia.

2. Naftifine: Naftifine is active against Trichophyton and Epidermophyton floccosum. Naftifine 1% cream and gel is used for topical treatment of tinea corporis, tinea cruris, and tinea pedis.

3. Butenafine: Butenafine is active against Trichophyton, Epidermophyton, and Malassezia. Butenafine 1% cream is used for topical treatment of tinea corporis, tinea cruris, interdigital tinea pedis, and tinea versicolor.

B. Griseofulvin

Griseofulvin has been largely replaced by oral terbinafine for the treatment of dermatophytic infections of the nails, although it is still used for ringworm and dermatophytosis of the skin and hair. Griseofulvin requires treatment of 6 to 12 months in duration. Griseofulvin accumulates in newly synthesized, keratin-containing tissue, where it causes disruption of the mitotic spindle and inhibition of fungal mitosis, and absorption is enhanced by high-fat meals. Griseofulvin induces hepatic CYP450 activity. It also increases the rate of metabolism of a number of drugs, including anticoagulants.

C. Nystatin

Nystatin is a polyene antibiotic, and its structure, chemistry, mechanism of action, and resistance profile resemble those of amphotericin B. Its use is restricted to topical treatment of Candida infections because of its systemic toxicity. The drug is negligibly
absorbed from the gastrointestinal tract, and it is never used parenterally. It is administered as an oral agent (“swish and swallow” or “swish and spit”) for the topical treatment of oral candidiasis. Excretion in the feces. Adverse effects are rare because of its lack of absorption orally, but nausea and vomiting occasionally occur.

D. Imidazoles

Imidazoles are azole derivatives, which currently include butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole, terconazole, and tioconazole. As a class of topical agents, they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida albicans, and Malassezia furfur, depending on the agent. Topical use is associated with contact dermatitis, vulvar irritation, and edema. Miconazole is a potent inhibitor of warfarin metabolism and has produced bleeding in warfarin-treated patients even when applied locally to the vaginal area. No significant difference in clinical outcomes is associated with any azole or nystatin in the treatment of vulvar candidiasis.

E. Ciclopirox

Ciclopirox inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and protein. Ciclopirox is active against Trichophyton, Epidermophyton, Microsporum, Candida albicans, and Malassezia. Ciclopirox 1% shampoo is used for treatment of seborrheic dermatitis. Ciclopirox 0.77% gel is used for treatment of interdigital tinea pedis, tinea corporis, and seborrheic dermatitis. Ciclopirox 8% solution is used for treatment of onychomycosis of nails without lanula involvement. Ciclopirox 0.77% cream and suspension is used for treatment of dermatomycosis, candidiasis, and tinea versicolor.

F. Tolnaftate

Tolnaftate distorts the hyphae and stunts mycelial growth in susceptible fungi. Tolnaftate is active against Epidermophyton, Microsporum, and Malassezia furfur. [Note: Tolnaftate is not effective against Candida.] Tolnaftate is used to treat tinea pedis, tinea cruris, and tinea corporis. It is available as a 1% solution, cream, and powder.