52 Antifungal Drugs

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DRUG LIST

Fungal infections are usually more difficult to treat than bacterial infections, because fungal organisms grow slowly and because fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents (e.g., devitalized or avascular tissues). Therapy of fungal infections usually requires prolonged treatment. Potentially life-threatening infections caused by dimorphic fungi are becoming more common because increasing numbers of immunocompromised patients are seen in clinical practice; AIDS, organ and bone marrow transplantation, and illnesses associated with neutropenia all predispose individuals to invasive fungal infection.

Superficial fungal infections involve cutaneous surfaces, such as the skin, nails, and hair, and mucous membrane surfaces, such as the oropharynx and vagina. A growing number of topical and systemic agents are available for the treatment of these infections. Deep-seated or disseminated fungal infections caused by dimorphic fungi, the yeasts *Cryptococcus neoformans,* and various *Candida* spp. respond to a limited number of systemic agents: amphotericin B desoxycholate (a polyene), amphotericin B liposomal preparations, flucytosine (a pyrimidine antimetabolite), the newer azoles, including ketoconazole, fluconazole, itraconazole and voriconazole, and capsofungin (an echinocandin).

AMPHOTERICIN B

Chemistry and Mechanism of Action

Amphotericin B (*Fungizone*), a polyene antifungal drug produced by the actinomycete *Streptomyces nodosus,* consists of a large ring structure with both hydrophilic

and lipophilic regions. Polyene antifungal drugs bind to the fungal cell membrane component ergosterol, leading to increased fungal cell membrane permeability and the loss of intracellular constituents. Amphotericin has a lesser affinity for the mammalian cell membrane component cholesterol, but this interaction does account for most adverse toxic effects associated with this drug.

Antifungal Spectrum

Amphotericin B is used to treat systemic disseminated fungal infections caused by *Candida* spp., *Cryptococcus neoformans,* and the invasive dimorphic fungi (*Aspergillus* spp., *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *Sporothrix schenckii*). Intravenous amphotericin B remains the treatment of choice for serious invasive fungal infections unresponsive to other agents.

The development of resistance during amphotericin B therapy is rarely clinically significant but has been reported; relative resistance expressed through alterations in membrane ergosterols has resulted in fungal isolates with reduced growth rates and reduced virulence. Infections with organisms intrinsically resistant to amphotericin B, such as *Candidia lusitaniae* and *Pseudallescheria boydii,* are uncommon but may be increasing in frequency.

Absorption, Distribution, Metabolism, and Excretion

Amphotericin B is primarily an intravenous drug; absorption from the intestinal tract is minimal. After infusion the drug is rapidly taken up by the liver and other organs and is then slowly released back into the circulation, where 90% of the drug is bound to protein. Its initial half-life is about 24 hours; the second elimination phase has a half-life of 15 days. The initial phase comprises elimination from both a central intravascular and a rapidly equilibrating extravascular compartment; the second, longer phase represents elimination from storage sites in a slowly equilibrating extravascular compartment.

Drug concentrations in pleural fluid, peritoneal fluid, synovial fluid, aqueous humor, and vitreous humor approach two-thirds of the serum concentration when local inflammation is present. Meningeal and amniotic fluid penetration, with or without local inflammation, is uniformly poor. Measurement of serum, urine, or cerebrospinal fluid drug levels has not been used clinically.

The major route of elimination of amphotericin B is by metabolism, with little intact drug detected in urine or bile. About 5% of amphotericin B is excreted in the urine as active drug, with drug still detectable in the urine 7 or more weeks after the last dose. Serum levels are not elevated in renal or hepatic failure, and the drug is not removed by hemodialysis.

Clinical Uses

Amphotericin B is most commonly used to treat serious disseminated yeast and dimorphic fungal infections in immunocompromised hospitalized patients. As additional experience has been gained in the treatment of fungal infections with the newer azoles, the use of amphotericin B has diminished; if azole drugs have equivalent efficacy, they are preferred to amphotericin B because of their reduced toxicity profile and ease of administration. For the unstable neutropenic patient with *Candida albicans* fungemia, amphotericin B is the drug of choice. For the stable nonneutropenic patient with *C. albicans* fungemia, fluconazole appears to be an acceptable alternative. For the AIDS patient with moderate to severe cryptococcal meningitis, amphotericin B appears to be superior to fluconazole for initial treatment; once infection is controlled, fluconazole in a daily oral dose is superior to and more convenient than weekly intravenous amphotericin B in the prevention of clinical relapses. For the AIDS patient with disseminated histoplasmosis, the treatment is similar; amphotericin B is preferred for the initiation of treatment, but once infection is controlled, daily oral itraconazole is preferred to intermittently dosed amphotericin B for suppression of chronic infection. Most forms of blastomycosis and sporotrichosis in normal hosts no longer require amphotericin B treatment.

Amphotericin B remains the drug of choice in the treatment of invasive aspergillosis, locally invasive mucormycosis, and many disseminated fungal infections occurring in immunocompromised hosts (the patient population most at risk for serious fungal infections). For example, the febrile neutropenic oncology patient with persistent fever despite empirical antibacterial therapy is best treated with amphotericin B for possible *Candida* spp. sepsis.

Adverse Effects

Fever, chills, and tachypnea commonly occur shortly after the initial intravenous doses of amphotericin B; this is not generally an allergic hypersensitivity to the drug, which is extremely rare. Continued administration of amphotericin B is accomplished by premedication with acetaminophen, aspirin, and/or diphenhydramine or the addition of hydrocortisone to the infusion bag.

Nephrotoxicity is the most common and the most serious long-term toxicity of amphotericin B administration. This drug reduces glomerular and renal tubular blood flow through a vasoconstrictive effect on afferent renal arterioles, which can lead to destruction of renal tubular cells and disruption of the tubular basement

membrane. Wasting of potassium and magnesium in the urine secondary to renal tubular acidosis usually results in hypokalemia and hypomagnesemia and necessitates oral or intravenous replacement of the minerals. Nephrotoxicity can be lessened by avoiding the concomitant administration of other nephrotoxic agents, such as aminoglycosides. Keeping patients well hydrated probably reduces nephrotoxicity; saline infusions prior to amphotericin B dosing have been advocated, and concomitant diuretic therapy should be avoided. Prolonging the infusion rate has been studied as a potential means of decreasing amphotericin B toxicity. Infusing the daily dose over 1 or 4 hours seems to make little difference, but recent data suggest that a continuous infusion of amphotericin B (giving the daily dose over 24 hours) decreases infusion-related adverse effects such as fever and also reduces nephrotoxicity. Increasing the dosing interval for amphotericin B to every other day may lessen nephrotoxicity *only* if the total dose of the drug delivered is reduced.

Normochromic normocytic anemia is the most common hematological side effect of amphotericin B administration; thrombocytopenia and leukopenia are much less common. Infusion of the drug into a peripheral vein usually causes phlebitis or thrombophlebitis. Nausea, vomiting, and anorexia are a persistent problem for some patients.

Lipid Formulations of Amphotericin B

Three lipid formulations of amphotericin B (amphotericin B colloidal dispersion: *Amphocil, Amphotec;* amphotericin B lipid complex: *Ablecet;* and liposomal amphotericin B: *Ambisome*) have been developed in an attempt to reduce the toxicity profile of this drug and to increase efficacy. Formulating amphotericin with lipids alters drug distribution, with lower levels of drug in the kidneys, reducing the incidence of nephrotoxicity. The lipid formulations appear to be equivalent to conventional amphotericin B both in the treatment of documented fungal infections and in the empirical treatment of the febrile neutropenic patient. While less toxic, the lipid formulations are significantly more expensive than conventional amphotericin B.

NYSTATIN

Nystatin (*Mycostatin*) is a polyene antifungal drug with a ring structure similar to that of amphotericin B and a mechanism of action identical to that of amphotericin B. Too toxic for systemic use, nystatin is limited to the topical treatment of superficial infections caused by *C. albicans.* Infections commonly treated by this drug include oral candidiasis (thrush), mild esophageal candidiasis, and vaginitis.

THE AZOLES

Azole antifungal drugs are synthetic compounds with broad-spectrum fungistatic activity. Azoles can be divided into two groups: the older imidazole agents, in which the five-member azole nucleus contains two nitrogens, and the newer triazole compounds, fluconazole and itraconazole, in which the azole nucleus contains three nitrogens.

All azoles exert antifungal activity by binding to cytochrome P450 enzymes responsible for the demethylation of lanosterol to ergosterol. Reduced fungal membrane ergosterol concentrations result in damaged, leaky cell membranes. The toxicity of these drugs depends on their relative affinities for mammalian and fungal cytochrome P450 enzymes. The triazoles tend to have fewer side effects, better absorption, better drug distribution in body tissues, and fewer drug interactions.

FLUCONAZOLE

Absorption, Distribution, Metabolism, and Excretion

Fluconazole (*Diflucan*) does not require an acidic environment, as does ketoconazole, for gastrointestinal absorption. About 80 to 90% of an orally administered dose is absorbed, yielding high serum drug levels. The half-life of the drug is 27 to 37 hours, permitting once-daily dosing in patients with normal renal function. Only 11% of circulating drug is bound to plasma proteins. The drug penetrates widely into most body tissues, including normal and inflamed meninges. Cerebrospinal fluid levels are 60 to 80% of serum levels, permitting effective treatment for fungal meningitis. About 80% of the drug is excreted unchanged in the urine, and 10% is excreted unchanged in the feces. Dosage reductions are required in the presence of renal insufficiency.

Clinical Uses

Fluconazole is very effective in the treatment of infections with most *Candida* spp. Thrush in the end-stage AIDS patient, often refractory to nystatin, clotrimazole, and ketoconazole, can usually be suppressed with oral fluconazole. AIDS patients with esophageal candidiasis also usually respond to fluconazole. A single 150-mg dose has been shown to be effective treatment for vaginal candidiasis. A 3-day course of oral fluconazole is effective treatment for *Candida* urinary tract infection and is more convenient than amphotericin B bladder irrigation. Preliminary findings suggest that *Candida* endophthalmitis can be successfully treated with fluconazole. Stable nonneutropenic patients with candidemia can be adequately treated with fluconazole, but unstable, immunosuppressed patients should initially receive

amphotericin B. *Candida krusei* isolates may be resistant to fluconazole.

Fluconazole may be an acceptable alternative to amphotericin B in the initial treatment of mild cryptococcal meningitis, and it has been shown to be superior to amphotericin B in the long-term prevention of relapsing meningitis (such patients require lifelong treatment.). Coccidioidal meningitis, previously treated with both intravenous and intrathecal amphotericin B, appears to respond at least as well to prolonged oral fluconazole therapy. Aspergillosis, mucormycosis, and pseudallescheriasis do not respond to fluconazole treatment. Sporotrichosis, histoplasmosis, and blastomycosis appear to be better treated with itraconazole, although fluconazole does appear to have significant activity against these dimorphic fungi.

A significant decrease in mortality from deep-seated mycoses was noted among bone marrow transplant recipients treated prophylactically with fluconazole, but similar benefits have not been seen in leukemia patients receiving prophylactic fluconazole. Fluconazole taken prophylactically by end-stage AIDS patients can reduce the incidence of cryptococcal meningitis, esophageal candidiasis, and superficial fungal infections.

Adverse Effects

Fluconazole is well tolerated. Nausea, vomiting, abdominal pain, diarrhea, and skin rash have been reported in fewer than 3% of patients. Asymptomatic liver enzyme elevation has been described, and several cases of drug-associated hepatic necrosis have been reported. Alopecia has been reported as a common adverse event in patients receiving prolonged high-dose therapy. Coadministration of fluconazole with phenytoin results in increased serum phenytoin levels.

ITRACONAZOLE

Absorption, Distribution, Metabolism, and Excretion

Although itraconazole and fluconazole are both triazoles, they are chemically and pharmacologically distinct. Itraconazole (*Sporanox*) is lipophilic and water insoluble and requires a low gastric pH for absorption. Oral bioavailability is variable, only 50 to 60% when taken with food and 20% or less when the drug is taken on an empty stomach. Itraconazole is highly protein bound (99%) and is metabolized in the liver and excreted into the bile. With initial dosing, the plasma half-life is 15 to 20 hours; steady-state serum concentrations are reached only after 2 weeks of therapy, when the half-life is extended to 30 to 35 hours. In lipophilic tissues, drug concentration is 2 to 20 times that found in serum. Drug does not appear in significant quantities in the urine and cannot be measured in spinal fluid.

Clinical Uses

Itraconazole is most useful in the long-term suppressive treatment of disseminated histoplasmosis in AIDS and in the oral treatment of nonmeningeal, non–life-threatening blastomycosis. It appears to be the drug of choice for all forms of sporotrichosis except meningitis and may have a lower relapse rate in the treatment of disseminated coccidioidomycosis than does fluconazole.

Itraconazole has replaced ketoconazole as the drug of choice in the treatment of paracoccidioidomycosis and chromomycosis, based on its lower toxicity profile. Efficacy has also been reported in the treatment of invasive aspergillosis.

Despite negligible cerebrospinal fluid concentrations, itraconazole shows promise in the treatment of cryptococcal and coccidioidal meningitis. Additional uses for itraconazole include treatment of vaginal candidiasis, tinea versicolor, dermatophyte infections, and onychomycosis. Fungal nail infections account for most use of this drug in the outpatient setting.

Adverse Effects

Itraconazole is usually well tolerated but can be associated with nausea and epigastric distress. Dizziness and headache also have been reported. High doses may cause hypokalemia, hypertension, and edema. Itraconazole, unlike ketoconazole, is not associated with hormonal suppression. Hepatotoxicity occurs in fewer than 5% of cases and is usually manifested by reversible liver enzyme elevations.

Drug Interactions

Itraconazole has significant interactions with a number of commonly prescribed drugs, such as rifampin, phenytoin, and carbamazepine. Itraconazole raises serum digoxin and cyclosporine levels and may affect the metabolism of oral hypoglycemic agents and coumadin. Absorption of itraconazole is impaired by antacids, H_2 blockers, proton pump inhibitors, and drugs that contain buffers, such as the antiretroviral agent didanosine.

KETOCONAZOLE

Absorption, Distribution, Metabolism, and Excretion

Unlike other imidazoles, ketoconazole (*Nizoral*) can be absorbed orally, but it requires an acidic gastric environment; patients concurrently treated with H_2 blockers or who have achlorhydria have minimal drug

absorption. Serum protein binding exceeds 90%. The drug is metabolized in the liver and excreted in the bile. The initial half-life of ketoconazole is 2 hours; 8 to 12 hours after ingestion, the half-life increases to 9 hours.

Reductions in renal and hepatic function do not alter plasma drug concentrations, and ketoconazole is not removed by hemodialysis or peritoneal dialysis. Penetration into cerebrospinal fluid is negligible, so that ketoconazole is ineffective in the treatment of fungal meningitis. Since only small amounts of active drug appear in the urine, ketoconazole is not effective in the treatment of *Candida* cystitis.

Clinical Uses

Ketoconazole remains useful in the treatment of cutaneous and mucous membrane dermatophyte and yeast infections, but it has been replaced by the newer triazoles in the treatment of most serious *Candida* infections and disseminated mycoses. Ketoconazole is usually effective in the treatment of thrush, but fluconazole is superior to ketoconazole for refractory thrush. Widespread dermatophyte infections on skin surfaces can be treated easily with oral ketoconazole when the use of topical antifungal agents would be impractical. Treatment of vulvovaginal candidiasis with topical imidazoles is less expensive.

Blastomycosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, and chromomycosis are better treated with itraconazole than ketoconazole, although ketoconazole remains an alternative agent. Ketoconazole is ineffective in the treatment of cryptococcosis, aspergillosis, and mucormycosis. Candidemia is best treated with fluconazole or amphotericin B.

Adverse Effects

Nausea, vomiting, and anorexia occur commonly with ketoconazole, especially when high doses are prescribed. Epigastric distress can be reduced by taking ketoconazole with food. Pruritis and/or allergic dermatitis occurs in 10% of patients. Liver enzyme elevations during therapy are not unusual and are usually reversible. Severe ketoconazole-associated hepatitis is rare.

At high doses, ketoconazole causes a clinically significant reduction in testosterone synthesis and blocks the adrenal response to corticotropin. Gynecomastia, impotence, reduced sperm counts, and diminished libido can occur in men, and prolonged drug use can result in irregular menses in women. These hormonal effects have led to the use of ketoconazole as a potential adjunctive treatment for prostatic carcinoma.

Drug Interactions

Both rifampin and isoniazid lower plasma ketoconazole levels, and concomitant administration should be avoided. Phenytoin serum levels should be monitored closely when ketoconazole is prescribed. Ketoconazole causes increases in serum concentrations of warfarin, cyclosporine, and sulfonylureas. Because of its ability to increase serum cyclosporine levels, ketoconazole has been given to cyclosporine-dependent cardiac transplant recipients to reduce the dose of cyclosporine needed and as a cost-saving measure.

MICONAZOLE

Miconazole (*Monistat*) is a broad-spectrum imidazole antifungal agent used in the topical treatment of cutaneous dermatophyte infections and mucous membrane *Candida* infections, such as vaginitis. Minimal absorption occurs from skin or mucous membrane surfaces. Local irritation to skin and mucous membranes can occur with topical use; headaches, urticaria, and abdominal cramping have been reported with treatment for vaginitis.

CLOTRIMAZOLE

Clotrimazole (*Lotrimin, Gyne-Lotrimin, Mycelex*) is a broad-spectrum fungistatic imidazole drug used in the topical treatment of oral, skin, and vaginal infections with *C. albicans.* It is also employed in the treatment of infections with cutaneous dermatophytes.

Topical use results in therapeutic drug concentrations in the epidermis and mucous membranes; less than 10% of the drug is systemically absorbed. Although clotrimazole is generally well tolerated, local abdominal cramping, increased urination, and transient liver enzyme elevations have been reported.

VORICONAZOLE

Voriconazole (*Vfend*), a derivative of fluconazole, is a second-generation triazole that has improved antifungal activity against *Aspergillus* and *Fusarium* spp., *P. boydii, Penicillium marneffei,* and fluconazole-resistant *Candida* spp. Like fluconazole, voriconazole has high oral bioavailability and good cerebrospinal fluid penetration, but unlike fluconazole, it undergoes extensive hepatic metabolism and is highly protein bound. No significant amount of bioactive drug is excreted into the urine. Dosage reduction is necessary with severe hepatic insufficiency but not with renal insufficiency.

Significant drug interactions include cyclosporins (increased cyclosporine levels), phenytoin, rifampin, and rifabutin (decreased voriconazole levels). Because of its low toxicity profile, this drug may gain importance in the chronic treatment of infections with invasive dimorphic fungi and resistant *Candida* spp.

OTHER IMIDAZOLES

A number of topical imidazoles are available for the treatment of cutaneous and mucous membrane candidiasis, ringworm, and tinea versicolor. Butoconazole (*Femstat*) is an effective topical agent for vaginal candidiasis; terconazole (*Terazol*) is effective in the treatment of vaginal candidiasis; and econazole (*Spectazole*) is useful in the treatment of superficial fungal infections of the skin, achieving high tissue levels in the stratum corneum. Oxiconazole nitrate (*Oxistat*) and sulconazole nitrate (*Exelderm*) are topical imidazole derivatives available for the treatment of dermatophyte infections and pityriasis (tinea versicolor). Tioconazole (*Vagistat*) is available without a prescription for the treatment of dermatophyte infections and candidiasis.

All of these agents have minimal systemic absorption when applied topically, but occasionally use of these drugs can result in systemic toxicity.

FLUCYTOSINE

Chemistry and Mechanism of Action

Flucytosine (5-flucytosine, 5-FC; *Ancoban*) is a fluorinated pyrimidine analogue of cytosine that was originally synthesized for possible use as an antineoplastic agent. 5-FC is converted to 5-fluorouracil inside the cell by the fungal enzyme cytosine deaminase. Subsequently, 5-FC metabolites interfere with fungal DNA synthesis by inhibiting thymidylate synthetase. Incorporation of these metabolites into fungal RNA may inhibit protein synthesis.

Absorption, Distribution, Metabolism, and Excretion

5-FC is well absorbed orally, with greater than 90% bioavailability. The serum half-life is 3 to 5 hours, with serum levels peaking 4 to 6 hours after a single dose. The drug is widely distributed in body fluids, with cerebrospinal fluid levels 60 to 80% of serum levels. The drug also penetrates well into urine, aqueous humor, and bronchial secretions. Minimal serum protein binding allows more than 90% of each dose to be excreted in the urine; significant dosage reductions are required in the presence of renal impairment. 5-FC can be removed by both hemodialysis and peritoneal dialysis. 5-FC conversion to toxic metabolites may occur in mammalian cells to a limited extent, which accounts for 5-FC toxicity.

Clinical Uses

Flucytosine has significant antifungal activity against *C. albicans,* other *Candida* spp., *C. neoformans,* and the fungal organisms responsible for chromomycosis. Not considered the drug of choice for these fungal infections, *5-FC does remain useful as part of combination therapy for systemic candidiasis and cryptococcal meningitis and as an alternative drug for chromomycosis.* When it is used as monotherapy, resistance and clinical failure are common. Potential mechanisms for drug resistance include decreased fungal cell membrane permeability and reduced levels of fungal cytosine deaminase. Combination therapy with amphotericin B and flucytosine in the treatment of cryptococcal meningitis and deep-seated *Candida* infections, such as septic arthritis and meningitis, permits reduced dosing of amphotericin B and prevents the emergence of 5-FC resistance. When higher doses of amphotericin B are used, combination therapy with 5-FC confers no additional clinical benefit except in the treatment of *Candida* endophthalmitis, where tissue penetration remains problematic.

Adverse Effects

When 5-FC is prescribed alone to patients with normal renal function, skin rash, epigastric distress, diarrhea, and liver enzyme elevations can occur. When it is prescribed to patients with renal insufficiency or to patients receiving concurrent amphotericin B therapy, blood levels of 5-FC may rise, and bone marrow toxicity leading to leukopenia and thrombocytopenia is common. 5-FC serum levels should be closely monitored in patients with renal insufficiency. Because of baseline leukopenia, 5-FC is often not tolerated by end-stage HIV-infected patients with disseminated fungal infection.

CAPSOFUNGIN

Capsofungin (*Cancidas*) is a semisynthetic lipopeptide known as an echinocandin, the first representative of a new class of antifungal agents that inhibit the synthesis of β-(1,3)-D-glucan, a cell wall component of filamentous fungi. Capsofungin has in vitro activity against *Aspergillus fumigatus, Aspergillus flavus,* and *Aspergillus terreus;* it is approved for the treatment of invasive aspergillosis in patients not responding to other antifungal agents, such as amphotericin B, lipid formulations of amphotericin B, and itraconazole. Additional indications for the use of this drug await further clinical study.

Capsofungin is not absorbed from the gastrointestinal tract. It is highly protein bound and has a serum half-life of 9 to 11 hours. Capsofungin appears to undergo liver metabolism and is not excreted in the urine. Adverse effects are mediated through histamine release; they include facial flushing, rash, fever, and pruritis. Nausea and vomiting have also been reported. Dose reductions are required in the presence of moderate hepatic insufficiency.

ALLYLAMINES

The allylamines (naftifine hydrochloride and terbinafine hydrochloride) are reversible noncompetitive inhibitors of the fungal enzyme squalene monooxygenase (squalene 2,3-epoxidase), which coverts squalene to lanosterol. With a decrease in lanosterol production, ergosterol production is also diminished, affecting fungal cell membrane synthesis and function. These agents generally exhibit fungicidal activity against dermatophytes and fungistatic activity against yeasts.

Naftifine hydrochloride (*Naftin*) is available for topical use only in the treatment of cutaneous dermatophyte and *Candida* infections; it is as effective as topical azoles for these conditions.

Terbinafine hydrochloride (*Lamisil*) is available for topical and systemic use (oral tablet) in the treatment of dermatophyte skin and nail infections. Terbinafine also exhibits in vitro activity against filamentous and dimorphic fungi, but its clinical utility in treating infections with these organisms has not yet been established. It is used most commonly in the treatment of onychomycosis; in this setting, terbinafine is superior to griseofulvin and at least equivalent to itraconazole. When given systemically, terbinafine is 99% protein bound and accumulates in fat, skin, and nails, persisting for weeks. Cerebrospinal fluid penetration is less than 10%. Dosage reductions are required with renal or hepatic insufficiency. Although terbinafine has little effect on hepatic cytochrome P450 enzyme systems, it does minimally enhance cyclosporine clearance. Oral terbinafine is generally well tolerated but occasionally causes gastric distress and liver enzyme elevation.

GRISEOFULVIN

Griseofulvin (*Gris-PEG, Grifulvin, Grisactin, Fulvicin*) is an oral fungistatic agent used in the long-term treatment of dermatophyte infections caused by *Epidermophyton, Microsporum,* and *Trichophyton* spp. Produced by the mold *Penicillium griseofulvin,* this agent inhibits fungal growth by binding to the microtubules responsible for mitotic spindle formation, leading to defective cell wall development.

Ineffective topically, griseofulvin is administered orally but has poor gastrointestinal absorption; absorption can be improved by microcrystalline processing of the drug and by taking the drug with fatty meals. Peak serum levels occur 4 hours after dosing. Griseofulvin is metabolized in the liver and has a half-life of 24 to 36 hours. The drug binds to keratin precursor cells and newly synthesized keratin in the stratum corneum of the skin, hair, and nails, stopping the progression of dermatophyte infection.

In the treatment of ringworm of the beard, scalp, and other skin surfaces, 4 to 6 weeks of therapy is often required. Therapy failure may be to the result of an incorrect diagnosis; superficial candidiasis, which may resemble a dermatophyte infection, does not respond to griseofulvin treatment. Onychomycosis responds very slowly to griseofulvin (1 year or more of treatment is commonly required) and cure rates are poor; itraconazole and terbinafine hydrochloride are more effective than griseofulvin for onychomycosis.

Griseofulvin is usually well tolerated. Headache is common with initiation of therapy. Hepatotoxicity (especially in patients with acute intermittent porphyria), dermatitis, and gastrointestinal distress also occur. Griseofulvin increases warfarin metabolism, and griseofulvin metabolism is increased by phenobarbital.

MISCELLANEOUS TOPICAL ANTIFUNGAL AGENTS

Ciclopirox olamine (*Loprox*) is a pyridone derivative available for the treatment of cutaneous dermatophyte infections, cutaneous *C. albicans* infections, and tinea versicolor caused by *Malassezia furfur.* It interferes with fungal growth by inhibiting macromolecule synthesis.

Tolnaftate (*Tinactin,* others) is a nonprescription antifungal agent effective in the topical treatment of dermatophyte infections and tinea. The mechanism of action is unknown.

Other older, less effective topical antifungal agents still available include undecylenic acid (*Desenex,* others). Used in the treatment of topical dermatophytes, undecylenic acid is fungistatic, requires prolonged administration, and is associated with a high relapse rate. *Desenex,* containing 5% undecylenic acid and 20% zinc undecylenate, is effective in the prevention of recurrent tinea pedis.

Study Questions

1. A 65-year-old man with acute leukemia recently underwent induction chemotherapy and subsequently developed neutropenia and fever (with no source of fever identified). Fever persisted despite the use of empirical antibacterial therapy, and amphotericin B has been prescribed for possible fungal sepsis. Which laboratory test is LEAST helpful in monitoring for toxicities associated with amphotericin B?
   (A) Liver function tests
   (B) Serum potassium
   (C) Serum magnesium
   (D) Serum blood urea nitrogen and creatinine
   (E) Hemoglobin and hematocrit
2. A 55-year-old obese woman with adult-onset diabetes mellitus has been receiving amoxicillin for treatment of an acute exacerbation of chronic bronchitis. After a week of therapy, the patient develops dysuria and increased urinary frequency. Urinalysis shows 10 to 50 white blood cells per high-power field, and Gram stain of urine shows many budding yeasts. Which antifungal agent would be best in treating this patient for *Candida* cystitis?
   (A) Oral ketoconazole
   (B) Oral fluconazole
   (C) Topical clotrimazole
   (D) Oral 5-flucytosine
   (E) Oral itraconazole
3. A 43-year-old woman recently underwent allogeneic bone marrow transplantation after chemotherapy failed in the treatment of metastatic breast carcinoma. The patient has had a stormy hospital course after her transplant, with respiratory failure requiring mechanical ventilation. A month into her hospitalization, surveillance sputum cultures reveal *Aspergillus fumigatus,* and a new infiltrate appears on her chest radiograph. Which antifungal agent is recommended for the treatment of invasive pulmonary aspergillosis in this patient?
   (A) Fluconazole
   (B) Amphotericin B
   (C) Amphotericin B with 5-flucytosine
   (D) Capsofungin
   (E) Itraconazole
4. A 57-year-old man with extensive onychomycosis (fungal toenail infection) asks you for an evaluation. He requests a prescription for itraconazole for treatment of this problem after seeing a television advertisement for this drug. He has chronic heartburn attributed to gastroesophageal reflux disease and is treated with the proton pump inhibitor omeprazole. He is taking lovastatin for treatment of hyperlipidemia. Three years ago he underwent cadaveric renal transplantation for end-stage kidney disease secondary to polycystic kidney disease and is taking cyclosporin to prevent transplant rejection. In prescribing itraconazole for this patient, what adjustments in his medication regimen do you recommend?
   (A) Discontinue omeprazole and substitute the H2 blocker ranitidine.
   (B) Discontinue omeprazole and substitute liquid antacids.
   (C) Discontinue omeprazole.
   (D) Continue lovastatin.
   (E) Increase cyclosporin dosing.

ANSWERS

1. **A.** Nephrotoxicity is the most common and most serious toxicity associated with amphotericin B administration. This is manifested by azotemia (elevated serum blood urea nitrogen and creatinine), and by renal tubular acidosis, which results in the wasting of potassium and magnesium in the urine (leading to hypokalemia and hypomagnesemia, requiring oral or intravenous replacement therapy). Normochromic normocytic anemia is also seen with long-term amphotericin B administration. Elevation of liver enzymes is not associated with the use of amphotericin B.
2. **B.** Oral fluconazole is well absorbed from the gastrointestinal tract, and 80% of drug is excreted into the urinary tract, allowing effective treatment of *Candida* cystitis. Subtherapeutic concentrations of itraconazole and ketoconazole are excreted into the urine; these agents are not effective in the treatment of *Candida* cystitis. Topical clotrimazole would be effective in the treatment of *Candida* vaginitis, which can cause dysuria, but would not be an effective treatment for cystitis. While 90% of 5-flucytosine is excreted unchanged in the urine, this more toxic agent is usually used only in combination therapy with a second antifungal agent (usually amphotericin B) in the treatment of systemic candidiasis or cryptococcal meningitis.
3. **B.** Amphotericin B remains the drug of choice in the treatment of disseminated or invasive fungal infections in immunocompromised hosts; bone marrow transplant recipients are the most heavily immunocompromised patients encountered in the hospital setting. 5-Flucytosine has no significant activity against *Aspergillus* spp., and it has bone marrow toxicity as a common adverse effect; it should

not be used in this setting. Fluconazole has not been shown to be effective in the treatment of aspergillosis. Itraconazole has been reported to be effective as salvage treatment in patients with aspergillosis if amphotericin B therapy fails; it should not be used as initial treatment in this setting. Capsofungin, a new echinocandin antifungal agent recently approved by the U. S. Food and Drug Administration for the treatment of refractory aspergillosis when standard therapy with amphotericin B fails, should also not be used to treat invasive aspergillosis until more data showing efficacy are available.

4. **C.** Patients receiving multiple medications may have adverse drug reactions when a new medication is added to the regimen. Itraconazole requires an acidic gastric environment for absorption; any drug reducing gastric acid production (H_2 blockers, proton pump inhibitors) or neutralizing gastric acid (antacids) will significantly reduce itraconazole absorption. Itraconazole inhibits the metabolism of lovastatin and simvastatin and should not be prescribed with these β-hydroxy-β-methyglutaryl–coenzyme A reductase inhibitors. Itraconazole will raise serum cyclosporin levels, resulting in cyclosporin toxicity, unless cyclosporin levels are closely monitored with dose reductions as indicated.

SUPPLEMENTAL READING

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CASE Study Chronic Disseminated Candidiasis

A 56-year-old man was admitted to the hospital for initiation of chemotherapy for acute myelogenous leukemia. Several weeks after completing induction chemotherapy, he developed profound neutropenia (absolute granulocyte count of less than 100 cells per milliliter, normal 800–9400), a known complication of chemotherapy. The patient received granulocyte-monocyte colony stimulating factor (GM-CSF), but neutropenia persisted; he then had a temperature elevation to 103°F (39.4°C). The patient received ceftazidime as empirical coverage for gram-negative sepsis. Vancomycin empirical coverage was added 2 days later as high fever persisted. Despite antibacterial coverage, high fevers continued, and 3 days later the patient began empirical therapy with amphotericin B for possible fungal sepsis. With the addition of amphotericin B, the patient appeared to improve clinically, with less fever. However, the patient remained profoundly neutropenic for the next several weeks. He required supplemental intravenous potassium and magnesium to replace electrolytes lost in the urine to amphotericin B–induced renal tubular acidosis. When his serum creatinine rose to 2.5 mg/dL, amphotericin B was discontinued, and a lipid formulation of amphotericin B was substituted; renal function stabilized and then improved slightly. After 4 weeks of profound neutropenia, the patient was noted to have a rapid rebound in granulocyte count. However, the patient once again developed high fever and appeared ill. Liver function tests revealed an elevation in serum transaminases. A computed tomographic scan of the abdomen revealed multiple small low-density lesions in the liver and spleen. Antifungal therapy with a lipid formulation of amphotericin B was continued. The patient had a

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stormy course requiring 4 additional weeks of antifungal therapy. Eventually the patient's liver enzymes returned to normal and follow-up abdominal computed tomography showed resolution of hepatic and splenic abscesses. He was discharged home after a 2- month hospitalization. What happened?

ANSWER: Chronic disseminated candidiasis (hepatosplenic candidiasis) occurs in patients with profound neutropenia. This patient was appropriately treated for possible fungal sepsis when antibacterial therapy failed to resolve fever in the setting of neutropenia. Despite therapy, however, the patient did have disseminated candidiasis, which persisted in a subclinical state during the long period of neutropenia. Once neutropenia resolved and the patient could generate an inflammatory response, fever reappeared and the patient worsened clinically. A new elevation in serum transaminases provided the clue that led to abdominal imaging and the detection of abscesses in the liver and spleen. The diagnosis of chronic disseminated candidiasis is often not confirmed by blood culture; the yield of blood cultures in the detection of candidemia is poor, with up to 50% of blood cultures falsely negative in this setting. Chronic disseminated candidiasis in neutropenic leukemia patients is a life-threatening infection with significant morbidity and mortality.