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Antifungal Pharmacology: A Review.

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Review Article

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ABSTRACT

The incidence and spectrum of local as well as systemic fungal infections have increased dramatically over the past two decades. Various factors which predispose patient to invasive fungal infections are advances in medical technology, use of invasive monitoring devices, mechanical ventilation, parenteral nutrition, broad spectrum antimicrobial agents, intensive cancer chemotherapies, corticosteroid and other immunosuppressive. Traditionally, many invasive fungal infections were associated with a poor prognosis, because effective therapeutic options were limited. The recent development of new antifungal agents has significantly contributed to the successful treatment of fungal diseases. These drugs offer novel mechanisms of action and expanded spectrums of activity over traditional treatment options. However, with these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs. Therefore, an understanding of the pharmacokinetic and pharmacodynamic properties of the classes of antifungal compounds is vital for the effective management of invasive fungal infections. This review provides a summary of the pharmacologic principles involved in treatment of fungal diseases.

INTRODUCTION

Classification of Antifungal Drugs

A. Systemic Antifungal Drugs

1. Polyenes antibiotics

   • Amphotericin B

2. Azole derivatives

   a) Imidazole: Ketoconazole, Miconazole
   b) Triazole: Fluconazole, Itraconazole, Voriconazole, Posaconazole, Ravuconazole

3. Echinocandin

   Capsofungin, Anidulafungin, Micafungin

4. Antimetabolite

Flucytosine (5-FC)
5. Nikkomycin

B. Topical Antifungal drugs

1. Polyene antibiotics: Amphotericin B, Nystatin, Hamycin, Natamycin (Pimaricin), Rimocidin, Hitachimycin, Filipin
2. Azoles–Imidazole: Clotrimazole, Ketoconazole, Miconazole, Econazole, Butaconazole, Oxiconazole, Sulconazole, Fenticonazole, Isoconazole, Bifonazole, Tiaconazol, Terconazole
3. Others: Tolnaftate, Undecyclinic acid, Povidone iodine, Triacetin, Gentian violet, Sodium thiosulphate, Cicloporox olamine, Benzoic acid, Quinidochlor

C. Systemic antifungal drugs for superficial infections

1. Heterocyclic benzofurans: Corticofunvin, Griseofulvin
2. Allylamine: Terbinafine, Butenafine, Naftifine.

Classification of Human Fungal Infections

Fungal infection	Site infected	Example
Superficial	Outermost skin and hair	Malasseziasis
Cutaneous	Deep epidermis and nails	Dermatophytosis
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis
Systemic opportunistic		Candidiasis, Aspergillosis, Cryptococcosis, Mucormycosis
Non-opportunistic		Histoplasmosis, Blastomycosis, Coccidiodomycosis

The number of agents available to treat invasive fungal infections has increased by 30% since the turn of the millennium. Although that statistic is impressive, it brings the total number of approved systemic antifungal drugs to only 14[1], with the potential for 1 more product to possibly emerge this year. These recent additions have provided clinicians with a tool previously lacking in the management of these life-threatening infections: therapeutic alternatives.

Along with new options, however, comes the need to understand the uniqueness of each agent, including its role in therapy, toxicity profile, and interactions with concomitant medications. To attain the maximum effect from these agents, clinicians should also become familiar with strategies to optimize efficacy through an understanding of pharmacokinetic and pharmacodynamic properties. These characteristics are unique for each class of antifungal drug and even for each member within a class. In many cases, this variability is not subtle and merits careful attention.

An additional concern related to the increasing number of antifungal drugs is the rapid increase in expenditures associated with their use. Many institutions throughout the United States are struggling with the increased financial burden related to the prescribing of these antifungal drugs [2]. Optimization of therapies through targeted application of various kinetic and dynamic principles may be one strategy to maximize the cost-effectiveness of treatment of invasive fungal infections. This review focuses on the pharmacologic principles involved in treatment of fungal disease and compares and contrasts the differences among the available agents. Given its role as an agent used primarily to treat superficial infections, terbinafine will not be included in this discussion.

History and Mechanisms of Action

Amphotericin B has been the mainstay of antifungal therapy since its release in the 1950s [3]. This agent emerged as the preferred polyene over the more toxic agent in this class, nystatin. Nystatin has since been relegated to topical and localized therapy because of its unfavorable adverse effect profile. The polyene agents exert their antifungal activity via binding to ergosterol in the fungal cell membrane. This disrupts cell permeability and results in rapid cell death [4]. To date, amphotericin B remains the broadest-spectrum antifungal agent available, with activity against many clinically relevant yeasts and moulds. During the 1990s, newer lipid preparations of amphotericin B, including amphotericin B lipid complex (Abelcet; Enzon), liposomal amphotericin B (AmBisome; Astellas Pharma US), and amphotericin B colloidal dispersion (Amphotec; Three Rivers Pharmaceuticals) were developed to alleviate drug toxicity [5]. These agents possess the same spectrum of activity as does amphotericin B deoxycholate. Each agent has been shown to decrease nephrotoxicity in comparison with the conventional preparation of amphotericin B [6]. However, with the exception of findings for histoplasmosis, data supporting increased efficacy of the lipid products against common opportunistic fungal pathogens are lacking [7].

Comparative pharmacokinetics of the antifungal agents.

Fluconazole is readily absorbed, with oral bioavailability easily achieving concentrations equal to 90% of those achieved by intravenous administration [9]. Absorption is not affected by food consumption, gastric pH, or disease state [10, 11]. Variable gastrointestinal absorption does occur with the other members of this class, however, and, for one compound (itraconazole), it varies according to the specific formulation. Oral bioavailability of these agents can be also be affected by food consumption and changes in gastric pH.

Itraconazole capsules demonstrate optimal absorption in the presence of gastric acid and, therefore, cannot be coadministered with agents known to raise gastric pH, such as H_2 receptor antagonists or proton pump inhibitors [26, 27]. Furthermore, itraconazole capsules should be administered after a full meal to optimize absorption [28]. In general, the cyclodextrin solution is more efficiently absorbed (i.e., the area under the concentration curve [AUC] is increased by 30%) than is the capsule formulation [12]. In addition, antacid therapy does not have a negative effect on absorption [13, 29]. Food can decrease serum concentrations of itraconazole solution; therefore, this preparation should be administered on an empty stomach [14, 15].

The oral bioavailability of voriconazole is >90% when the stomach is empty, but it decreases when food is present [16, 17]. Thus, this agent should be administered on an empty stomach. In contrast, posaconazole absorption is optimized when administered with a high-fat meal or a similar composition nutritional supplement, such as Boost Plus (Novartis Nutrition) [18].

Distribution

The distribution of antifungal agents in the body is another important factor to consider in the treatment of invasive fungal infections, because these infections may occur at physiologically sequestered sites. As demonstrated by relatively large volumes of distribution, the available antifungal agents are widely distributed throughout the body, with a few significant exceptions discussed below [9, 13, 17, 19, 20]. The main factors affecting drug distribution are molecular size, charge, degree of protein binding, and route of elimination.

Fungal infections of the CNS are associated with high morbidity and mortality and are difficult to treat. Many antifungal agents have large molecular weights that preclude their ability to penetrate the blood-brain barrier and achieve therapeutic CSF concentrations. Currently, flucytosine, fluconazole, and voriconazole have the best CSF penetration, with each resulting in concentrations of at least 50% of those seen in serum [21, 30, 31]. The concept of CSF concentrations predicting the efficacy of antifungal agents for CNS infections is a bit misleading. For example, amphotericin B, a drug that is essentially undetectable in CSF, has been the mainstay of treatment for cryptococcal meningitis, despite the lack of detectable drug concentrations in the CSF [8, 32]. In these instances, it is postulated that tissue concentrations of these agents are adequate to allow efficacy. Recent investigations have suggested that brain parenchymal concentrations of the azole agents and echinocandins may be more meaningful for prediction of therapeutic response.

Ophthalmologic fungal infections are also difficult to treat. Traditionally, topical therapies have been used for these infections, especially when the disease is limited to superficial infection. Many of the available systemic antifungal therapies can achieve intraocular concentrations adequate for treatment of more invasive disease. For other agents, localized therapy, such as intravitreal injections, is required for reliable concentrations within the vitreous body.

Relatively few available antifungal agents are renally eliminated as unchanged drug or active metabolite and, therefore, do not provide high concentrations of microbiologically active drug in the urine. Currently, fluconazole and flucytosine are the only drugs that can achieve reliable urine concentrations >50% of serum exposure when given systemically [20, 22]. It is important to note that, because many of these agents produce adequate tissue concentrations, a lack of detectable urine concentrations does not necessarily preclude use when the disease involves renal parenchyma.

The degree of protein binding is another characteristic that alters systemic exposure to drug; a protein-bound drug is not available for microbiologic activity. Thus, this factor plays an important role in determining the amount of active drug present at a given site of infection [33]. Unfortunately, the majority of available pharmacokinetic data for the antifungal agents reflect concentrations of total drug. Therefore, clinicians are left to hypothesize about the amount of measured drug actually available to fight infection (i.e., the portion of free, unbound drug). The polyene agents and many azole antifungals, with the exception of voriconazole and fluconazole, are highly protein bound (>90%). Protein binding with the echinocandin class varies from 85% to 99% for anidulafungin, caspofungin, and micafungin [4, 18, 19, 23,24,25, 34, 35].

The major protein that binds these drugs is albumin, although other serum proteins may also play a role [36, 37]. Many patients who are at risk for fungal infection are malnourished and, as a result, have low levels of serum

albumin. The effect of this on protein binding of drugs may result in higher concentrations of available or active drug; however, this concept has not been sufficiently studied with regard to a potential effect on antifungal drug dosing or efficacy [33, 38, 39,40].

Metabolism and elimination

Many systemic antifungal agents undergo some degree of hepatic metabolism before elimination. One notable exception is flucytosine, which is not known to be metabolized hepatically, because urine excretion of unchanged drug accounts for >90% of its elimination [20]. For the amphotericin B products, the exact routes of metabolism and elimination are largely unknown [4].

All azole antifungals undergo some degree of hepatic metabolism. For fluconazole, the role of metabolism in drug elimination is minimal, but this is not the case with itraconazole, voriconazole, and posaconazole, which are highly dependent on metabolism for drug elimination. Given that there are few active antifungal metabolites, this results in production of inactive compounds that provide no clinically meaningful activity, with the notable exception of hydroxyitraconazole (a metabolite of itraconazole) [41]. Although oxidative metabolism is the primary process involved in azole metabolism, glucuronide conjugation does occur with some of these drugs, especially posaconazole [42].

Each of the 2 available echinocandins (caspofungin and micafungin) undergoes metabolism to produce 2 distinct inactive metabolites. For caspofungin, these processes are hepatic hydrolysis and *N*-acetylation [43]. Micafungin undergoes nonoxidative metabolism to produce 2 distinct compounds [90]. Although it is a weak substrate for cytochrome P450 (CYP450), the metabolism of micafungin does not appear to be affected by inhibitors or substrates of this enzyme system. Unlike caspofungin and micafungin, anidulafungin is not hepatically metabolized but undergoes nonenzymatic degradation [45].

Effect of organ dysfunction on drug dosing

Although the various formulations of amphotericin B are known for their ability to cause nephrotoxicity, they do not require dose adjustment for patients with decreased renal function. In fact, of all the available systemic antifungal agents, only fluconazole and flucytosine require dosing modification when given to patients with decreased levels of creatinine clearance [4, 20]. In some instances, such as with amphotericin B, dosing regimens may be altered in attempts to ameliorate toxicity, but this is not done as a result of altered drug clearance. Another example is the cyclodextrins, which are present in the intravenous preparations of itraconazole and voriconazole and can accumulate in renal disease. Therefore, the use of these formulations in patients with creatinine clearance <50 mL/min, in the case of voriconazole, and 30 mL/min, in the case of itraconazole, is cautioned for these formulations [13, 17].

Comparative toxicities of antifungal agents

Amphotericin B preparations

The toxicity of amphotericin B is well known. In addition to the nephrotoxicity and acute infusion-related reactions associated with the drug, a unique pulmonary reaction can be seen, particularly with certain lipid preparations. With the liposomal preparation of amphotericin B, a triad of infusional toxicity has been characterized. This toxicity can manifest as a combination of the following clinical scenarios: pulmonary toxicity (i.e., chest pain, dyspnea, and hypoxia); abdominal, flank, or leg pain; or flushing and urticaria [49,50]. Similarly, with amphotericin B colloidal dispersion, severe hypoxia has been reported in patients; in one study, hypoxia occurred more commonly in association with the use of amphotericin B colloidal dispersion than with amphotericin B deoxycholate [51]. Hypoxia has also been reported in association with use of the lipid complex of amphotericin B. In one study, up to 20% of patients experienced this toxicity. Unique characteristics in this case included onset of symptoms beyond the second day of therapy for >70% of patients [46].

Azole antifungal agents

Fluconazole is an extremely well-tolerated agent that lacks significant toxicity, despite having been used for treatment and prophylaxis in many patient populations for more than a decade. However, reversible alopecia is not uncommon with this agent [52].

Oral itraconazole solution is also relatively safe but can be associated with nausea and diarrhea severe enough to force discontinuation. This reaction is caused by the excipient hydroxypropyl-β-cyclodextrin, which is used to increase solubility of the parent drug [53]. Itraconazole has been described as causing a unique triad of hypertension, hypokalemia, and edema, mostly in older adults [24]. A negative inotropic effect resulting in congestive

heart failure has also been described and has prompted changes to the package labeling to avoid administration of itraconazole to patients with a history of heart failure [13, 55].

Two unique adverse events have been associated with the use of voriconazole: visual disturbances and cutaneous phototoxicity. The mechanism for visual disturbances is not known but manifests itself as photopsia (i.e., the appearance of bright lights, color changes, or wavy lines) or abnormal vision in up to 45% of patients receiving the treatment [56]. This effect is usually mild and transient, and it abates with continued treatment. In addition, this effect appears to be associated with higher doses of voriconazole [47]. Rash has been reported in association with voriconazole use in up to 8% of subjects; phototoxicity-related rash occurs less frequently but is a significant problem for ambulatory patients [57, 58]. This effect is not prevented through the use of sunscreens but is reversible after discontinuation of therapy.

Posaconazole has been well tolerated in clinical trials to date. The most frequently reported adverse events attributed to the drug have been associated with hepatic toxicities. These toxicities seem to occur less frequently than with other members of the triazole class [48]. Fatal hepatotoxicity has been reported with itraconazole, voriconazole, and posaconazole. Therefore, close monitoring of hepatic function is warranted with all members of the azole class [13, 17].

Echinocandins

The echinocandins are associated with few toxicities, making them safe agents to administer. The most notable, yet uncommon, event reported is a histamine-mediated infusion-related reaction. As with vancomycin, this reaction can be relieved by slowing the rate of infusion or premedicating with an antihistamine, such as diphenhydramine.

CONCLUSION

Clinicians now have access to an expanded number of antifungal agents; however, the panacea of antifungal therapy remains to be found. Therefore, a keen appreciation of the properties associated with each antifungal agent is imperative in the selection and administration of antifungal therapy. Differences in the pharmacokinetics of each unique drug render effective administration a challenge, particularly given the complex regimens that patients who are at risk for fungal infection receive because of their underlying disease states. Toxicity profiles also play a major role in the treatment of fungal disease, and differences among the antifungal classes, as well as agents within a given class, must be understood. With judicious use of the available agents, we are able to successfully and safely treat a growing number of life-threatening infections.

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