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A REVIEW ON ANTIFUNGAL AGENTS

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ABSTRACT

There are currently few antifungals in use which show efficacy against fungal diseases. These antifungals mostly target specific components of fungal plasma membrane or its biosynthetic pathways. However, more recent class of antifungals in use is echinocandins which target the fungal cell wall components. The availability of mostly fungistatic antifungals in clinical use, often led to the development of tolerance to these very drugs by the pathogenic fungal species. Thus, the development of clinical multidrug resistance (MDR) leads to higher tolerance to drugs and its emergence is helped by multiple mechanisms. MDR is indeed a multifactorial phenomenon wherein a resistant organism possesses several mechanisms which contribute to display reduced susceptibility to not only single drug in use but also show collateral resistance to several drugs. Considering the limited availability of antifungals in use and the emergence of MDR in fungal infections, there is a continuous need for the development of novel broad spectrum antifungal drugs with better efficacy. Here, we briefly present an overview of the current understanding of the antifungal drugs in use, their mechanism of action and the emerging possible novel antifungal drugs with great promise.

INTRODUCTION

Fungal infections are caused by microscopic organisms that can invade the epithelial tissue. The fungal kingdom includes yeasts, molds, rusts and mushrooms. Fungi, like animals, are hetrotrophic, that is, they obtain nutrients from the environment, not from endogenous sources (like plants with photosynthesis). Most fungi are beneficial and are involved in biodegradation, however, a few can cause opportunistic infections if they are introduced into the skin through wounds, or into the lungs and nasal passages if inhaled.

Diseases caused by fungi include superficial infections of the skin by dermatophytes in the Microsporum, Trichophyton or Epidermophyton genera. These dermophytic infections are named for the site of infection rather than the causative organism.

Serial No.	Dermophytic Infection	Causative Organism
1.	Tinea corporis (ringworm)	Microsporum canis, Trichophyton mentagrophytes
2.	Tinea pedis (athlete's foot)	T. rubrum, T. mentagrophytes, Epidermophyton floccosum
3.	Tinea cruis (jock itch)	T. rubrum, T. mentagrophytes, E. floccosum
4.	Tinea capis (scalp)	M. canis T. tonsurans
5.	Tinea barbae (beard/hair)	T. rubrum, T. mentagrophytes
6.	Tinea unguium (nails)	T. rubrum, T. mentagrophytes, E. floccosum

Systemic infections are caused by the inhalation of spores and cause fungal pneumonia. This pneumonia cannot be transmitted from human to human. These infections can occur in otherwise healthy individuals. Many of the organisms that cause systemic fungal infections are confined to specific geographic locations due to favourable climates for their proliferation.

Serial No.	Systemic Infections	Causative Organism
1.	Coccidioidomycosis	Cocidioides immitis
2.	Brazilian Blastomycosis	Paracoccidioides brasiliensis
3.	Histoplasmosis	Histoplasma capsulatum
4.	Blastomycosis	Blastomyces dermatitidis

Organisms that cause opportunistic infections will not gain a foothold in healthy individuals, but in the immunocompromised they can cause serious, sometimes life-threatening infections. Patients especially susceptible to these infections include individuals with leukemia and other blood diseases, cancer, HIV and other immune deficiencies, and diabetes. These organisms can be found throughout the U.S.

Serial No.	Opportunistic Infections	Causative Organism	Target Organs
1.	Candidaisis, Thrush, Vulvovaginitis	Candida albicans	GI tract and vagina
2.	Pneumocystis carinii pneumonia	Pneumocystis carinii	Lungs
3.	Mucormycosis	Murcor sp.	Sinuses, eyes, blood and brain
4.	Aspergillosis	Aspergillus sp.	Lung, brain, sinuses and other organs
5.	Cryptococcal meningitis	Cryptococcus neoformans	Through inhalation, may cause mild lung infection. Mainly affects CNS

Biochemical Targets for Antifungal Chemotherapy

Fungal cells are complex organisms that share many biochemical targets with other eukaryotic cells. Therefore, agents that interact with fungal targets not found in eukaryotic cells are needed. The fungal cell wall is a unique organelle that fulfils the criteria for selective toxicity. The fungal cell wall differs greatly from the bacterial cell wall and is not affected by antibacterial cell wall inhibitors such as the β-lactams or vancomycin.

Arrangement of the biomolecular components of the cell wall accounts for the individual identity of the organism. Although, each organism has a different biochemical composition, their gross cell wall structure is similar. There are three general mechanisms of action for the antifungal agents: cell membrane disruption, inhibition of cell division and inhibition of cell wall formation.

Inhibition of Cell Wall Formation

Interference with fungal cell wall biosynthesis has not been as successful and effective as penicilins and cephalosporins against bacteria. Many chemicals have been discovered that interfere with various steps in fungal cell wall synthesis with excellent antifungal activity in vitro. Unfortunately, development of these agents into useful drugs has proven very difficult. Many of these agents are developed to target β-glucan synthesis.

Cell Membrane Disruption

Antifungal agents that disrupt the cell membrane do so by targeting ergosterol, either by binding to the sterol, forming pores and causing the membrane to become leaky (as with polyene antifungals), or inhibiting ergosterol biosynthesis (as seen with azole antifungal agents). Ergosterol is similar to mammalian cholesterol, thus agents binding ergosterol may have a cytotoxic effect in the host tissue. Ergosterol has two conjugated double bonds that are lacking in mammalian sterols.

Pharmacokinetics and Pharmacodynamics

The selection of an appropriate antifungal agent depends on multiple factors in addition to the spectrum of activity. As with antibacterial therapy, the routes of administration and elimination are often important considerations in selecting a drug. This is particularly true when the optimal therapy for a patient with a fungal infection is being determined. Alterations in gastrointestinal tract integrity, impaired renal or hepatic function, and limited intravenous access are frequent issues for patients who are at high risk of acquiring fungal disease.

Further complicating the clinical picture is the variability in available formulations among different antifungal agents. Many drugs are available only as intravenous preparations (e.g., amphotericin B preparations and echinocandin agents) or only as oral preparations (e.g., posaconazole and flucytosine) because of differences in solubility and oral bioavailability. For the agents that can be administered by multiple routes (e.g., fluconazole, itraconazole, and voriconazole), there are often difficulties in administration of these preparations because of toxicities, drug interactions, and variability with different product formulations. Therefore, it is important to have an appreciation of the differences among these drugs with regard to their pharmacokinetic properties, including absorption, distribution, metabolism, and excretion.

Absorption

Several of the antifungal agents, including the polyene and echinocandin classes, do not have appreciable oral bioavailability. Until the early 1990s, the lack of oral treatment options left intravenous therapy as the only alternative for the treatment of invasive fungal infections.

Fluconazole is readily absorbed, with oral bioavailability easily achieving concentrations equal to 90% of those achieved by intravenous administration. Absorption is not affected by food consumption, gastric pH, or disease state. 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. Furthermore, itraconazole capsules should be administered after a full meal to optimize absorption. 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. In addition, antacid therapy does not have a negative effect on absorption. Food can decrease serum concentrations of itraconazole solution; therefore, this preparation should be administered on an empty stomach.

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. 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.

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. For the amphotericin B products, the exact routes of metabolism and elimination are largely unknown. 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). Although oxidative metabolism is the primary process involved in azole metabolism, glucuronide conjugation does occur with some of these drugs, especially posaconazole.

Drug-drug interactions

The effect of antifungal agents on other therapeutic regimens merits serious consideration when therapy is being initiated or discontinued. Antifungal drugs can alter the safety or efficacy of concomitant therapies through several mechanisms. The first of these involves additive toxicities associated with concomitant administration; the most apparent example is nephrotoxicity caused by amphotericin B. This toxicity can enhance the renal effect of many other agents, including cyclosporine and the aminoglycosides.

A more complicated issue relates to the inhibition of drug metabolism that occurs as a result of these drug interactions. A complete review of CYP450-mediated drug interactions is beyond the scope of this article, but the importance of this effect should not be minimized. Because of their mechanism of action, all the azole antifungals inhibit CYP450 enzymes to some degree. As a result, careful consideration must be given when an azole agent is added to a patient's drug regimen. Similarly, when an azole agent is discontinued, the change in metabolism that occurs may have profound clinical implications. For example, organ rejection has been reported after discontinuation of an azole antifungal that was not accompanied by the necessary upward dose adjustments in the affected immunosuppressant agent.

Pharmacodynamics

Another important consideration in the optimization of antifungal treatment regimens is the interaction between the fungal pathogen, the antifungal agent, and host factors. These pharmacodynamic principles have not been described for antifungal agents with the same level of detail as for the antibacterial agents. However, fairly extensive in vitro and animal model investigations have been undertaken with agents from the triazole, polyene, and echinocandin antifungal classes.

A series of reports has defined the pharmacokinetic exposure of these compounds relative to the MIC of the infecting pathogen as a means of optimizing treatment efficacy. In animal models of disseminated candidiasis, killing of fungal organisms with echinocandins and polyenes is optimized by achieving peak drug concentrations 2–10-fold in excess of the MIC. Treatment outcome with the triazole antifungals has been shown to correlate with the drug exposure over time, which is similar to the concentration needed to inhibit the organism in vitro, or the MIC. The pharmacokinetic index that best accounts for the entire exposure over time is the ratio of the 24-h AUC to the MIC (24-h AUC: MIC). In preclinical infection models, a free drug 24-h AUC: MIC value near 25: 1 has been shown to reproducibly predict outcome with each of the triazole compounds. Examination of clinical trial data with Candida infections has suggested that this pharmacodynamic relationship is similarly helpful for prediction of treatment efficacy in humans. The clinical relevance of the relationships between a specific drug

exposure, the MIC, and outcome is less clear for other fungal pathogens and drug classes.

Toxicity

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 in fusional 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. 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. 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.

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.

Oral itraconazole solution is also relatively safe but can be associated with nausea and diarrhoea 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. Itraconazole has been described as causing a unique triad of hypertension, hypokalemia, and edema, mostly in older adults. A negative inotropic effect resulting in congestive heart failure has also been described and has prompted changes to the package labelling to avoid administration of itraconazole to patients with a history of heart failure.

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, colour changes, or wavy lines) or abnormal vision in up to 45% of patients receiving the treatment. 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. Rash has been reported in association with voriconazole use in up to 8% of subjects; photo toxicity-related rash occurs less frequently but is a significant problem for ambulatory patients. 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. 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.

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

The introduction of antifungal agents during the past decade has revolutionized the treatment of invasive mycoses. However, with these new therapies comes a need for increased awareness of the limitations in their spectrum of activity, pharmacokinetics, and risk for pharmacokinetic drug interactions. Newer broad-spectrum triazoles, in particular voriconazole and posaconazole, display significant variability in bloodstream concentrations from one patient to the next that may necessitate TDM in select situations to guide drug therapy and dosing. Long-term toxicities have become more of a concern because ambulatory patients with long-term immunosuppression are taking antifungal therapies for prolonged periods. For most patients, however, the benefits of safer and more effective antifungal therapy vastly outweigh the manageable risks of developing toxicity and undertreating a life-threatening systemic fungal infection.

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