Antifungal agents: Polyene, azole, antimetabolite, other and future agents

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Abstract

Antifungals have always been considered as one of the astonishing discoveries of the 20th century. This is correct, but the real marvel is the development of antifungal resistance in hospitals, communities, and the environment concomitant with their use. Fungal infections have emerged as an important clinical threat, with significant associated morbidity and mortality. This study is designed to provide a comprehensive view of antifungal agents and related agents. Information was based on the expertise of some literatures. Over the past decades, the incidence and diversity of fungal infection has grown in association with an increasing number of immunocompromised patients. An understanding of the pharmacokinetic and pharmacodynamics 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. Clinical needs for novel antifungal agents have altered steadily with the rise and fall of AIDS-related mycoses, and the change in spectrum of fatal disseminated fungal infections that has accompanied change in therapeutic immunosuppressive therapies.

Keywords: Antifungal agents, Future agents, Polyenes, Azole

Introduction

The development of an antifungal agents has lagged behind that of antibacterial agents. This is a predictable consequence of the cellular structure of the organisms involved. Bacteria are prokaryotic and hence offer numerous structural and metabolic targets that differ from those of the human host. Fungi, in contrast, are eukaryotes, and consequently most agent toxic to fungi are also toxic to the host. Furthermore, because fungi generally grow slowly and often in multicellular forms, they are more difficult to quantify than bacteria. This difficulty complicates experiments designed to evaluate the *in vitro* or *in vivo* properties of a potential antifungal agents (1). Despite these limitations, numerous advances have been made in developing new antifungal agents and in understanding the existing ones. Three groups of drugs are emphasized; the polyenes, the azoles, and antimetabolite.

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The increased use of antibacterial and antifungal agents in recent years has resulted in the development of resistance to these drugs (2).

Early treatment

Antifungal therapies evolved slowly during the early years of the past century. Potassium iodide was the standard treatment for cutaneous fungal infections including actinomycosis, blastomycosis, sporotrichosis, and tinea form the beginning of the 20th century until after the Second World War (3).

First derived from sea algae, potassium iodide was considered to exert a direct antifungal effect, although the complete mechanism of action remains unclear (4, 5). Contemporarily, radiation was used to treat severe tinea captis infections, often with significant complicate ions including skin cancer and brain tumors. In the 1940s, Mayer et al, Demonstrated that sulfonamide drugs, such as sulfadiazine, exhibited both fungistatic and fungicidal activities against *Histoplasma capsulatum* (6, 7).This discovery led to the formation and the use of sulfonamide derivative for the treatment of blastomycosis, nocardiosis, and cryptococcosis. Griseofulvin, a compound derived from *Penicillium griseofulvum*, has been widely used to treat superficial fungal infections since its isolation in 1939(8-10). An understanding of the mechanisms of action and *in vitro* profiles of antifungal agents is pivotal to selecting effective treatments for dermatophytosis. The principal mechanisms of action of antifungal drugs include disruption of spindle and cytoplasmic microtubule function (e.g., griseofulvin), depletion of or binding to ergosterol (e.g., terbinafine, ketoconazole, and amphotericin B), and accumulation of squalene (terbinafine). It is likely that antifungal agents that deplete or bind to ergosterol have fungistatic activity only; agents that produce a concomitant accumulation of intracellular squalene have fungicidal activity. Although the mechanism of action markedly influences the clinical efficacy of an antifungal agent, *in vitro* and *in vivo* antimycotic profiles and bioavailability factors such as drug access to the stratum corneum also contribute to the effectiveness of antifungal agents (11).

Meanwhile, six new antifungal agents have just reached, or are approaching, the clinic. Three are new triazoles, with extremely broad antifungal spectra, and three are echinocandins, which inhibit synthesis of fungal cell wall polysaccharides – a new mode of action. In addition, the sordarins represent a novel class of agents that inhibit fungal protein synthesis. This review describes the targets and mechanisms of action of all classes of antifungal agents in clinical use or with clinical potential (12) .

In 1985, Gentle reported the successful treatment of ringworm in guinea pigs using oral griseofulvin, the successful attempts to develop novel and effective antifungal drugs encouraged the further study and discovery of new agents (13).

Polyenes

Nystatin, amphotericin B, pimaricin**,** are polyenes drugs that bind to sterol components in the phospholipid-sterol membranes of fungal cells to form complexes that induce physical changes in the membrane. The number of conjugated bonds and the molecular size of a particular polyene macrolide influence its affinity for different sterols in fungal cell membranes. Amphotericin B has a greater affinity for fungal ergosterol, the major sterol in fungal membranes, than for eukaryotic (host) cell membrane cholesterol (14). The long polyene structure causes the formation of channels in the fungal cell membrane. The resultant loss of membrane permeability results in the loss of critically important molecules. Potassium ion efflux from the fungal cell and hydrogen ion influx cause internal acidification and a halt in enzymatic functions. Sugars and amino acids also eventually leak from an arrested cell. Fungistatic effects are most often evident at usual polyene concentrations. High drug concentrations and pH values

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between 6.0 and 7.3 in the surrounding medium may lead to fungicidal rather than fungistatic action (15).

Nystatin

In 1949, while conducting research at the Division of Laboratories and Research of the New York State Department of Health. It is derived from *Streptomyces noursei* (14). In 1955, Slome reported topical nystatin to be particularly effective for treatment of noninvasive candidiasis a frequent complication observed in children enrolled in early chemotherapeutic leukemia trials underway during this period (15, 16). Nystatin exhibited good activity against *candida* and modest activity against *Aspergillus* species. In aqueous solutions, nystatin forms aggregates that are toxic to mammalian cells both *in vitro* and *in vivo*. The insolubility and toxicity precluded its use as an intravenous therapy for systemic mycosis (17). Recently, a more soluble liposomal nystatin formulation (Nystran®) with reduced toxicity was developed (18).The liposomal formulation consists of a freeze-dried, solid dispersion of nystatin mixed with a dispersing agent such as a poloxamer or polysorbate. The dispersing agent prevents aggregate formation in solution, increasing the drug's solubility and decreasing toxicity while maintaining efficacy (19). Liposomal nystatin has good activity *in vitro* against a variety of *candida* species including some amphotericin B-resistant isolate (15-19). Although the liposomal form of nystatin was less toxic than conventional nystatin, unacceptable infusion-related toxicity unfortunately caused a halt in the development of this drug (20).

Amphotericin B

Amphotericin B is the mainstay antifungal agent for treatment of life-threatening mycosis and for most other mycosis, with possible exception of the dermatophytosis. This drug binds to the membrane sterols of fungal cells, causing impairment of their barrier function and loss of cell constituents. Metabolic disruption and cell death are consequent upon membrane alterations. Investigations of the sterol content of mutant strains of *Candida albicans* and *Cryptococcus neoformans* has demonstrated that resistance is often associated with alterations in membrane sterol composition (7, 21, 22). Discovered by gold in 1956, it can truly be said represent a gold standards, it broad spectrum of activity includes most of the medically important moulds and yeasts, including dimorphic pathogens such as *Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*. This antifungal agent of choice in treating most opportunistic mycoses caused by fungi such as *Candida* species, *Cryptococcus neoformans*, *Aspergillus* species and the *zygomycetes* (11-19) . Resistance to amphotericin B is rare, but is noteworthy for *Pesudallescheria boydii*, *Fusarium* spp, and *Trichosporon* spp. The drug must administered intravenously and is associated with numerous side effect, ranging from phlebitis at the infusion site and chills to renal toxicity, which may be severe. A major advance in the use of this agent has resulted from an understanding of the mechanism of its renal toxicity, which is presumed to involve tubuloglomerular feedback. The suppression of glomerular filtration could be reduced by administering sodium chloride (11-22).

Natamycin

Natamycin, also known as pimaricin and sometimes sold as Natacyn, is a naturally occurring antifungal agent produced during fermentation by the bacterium *Streptomyces natalensis*, commonly found in soil. Natamycin has a very low solubility in water, however, natamycin is effective at very low levels. There is an MIC (minimum inhibitory concentration) of less than 10 ppm for most molds. Natamycin is classified as a macrolide polyene antifungal and as a drug is used to treat fungal keratitis,

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an infection of the eye. This drug that natamycin acts via a novel mode of action and blocks fungal growth by binding specifically to ergosterol. It is especially effective against *Aspergillus* and *Fusarium* corneal infections (23).

Azole

The azole antifungal agents have five-membered organic rings that contain either two or three nitrogen molecules, such as imidazoles or the triazoles respectively. The clinically useful Imidazoles are Clotrimazole, Miconazole and Ketoconazole. Two important triazoles are Itraconazole and Fluconazole. Over all the azole antifungal agents are thought to inhibit cytochrome P_{450}-dependent enzyme involved in the biosynthesis of cell membrane sterols. Ketoconazole set the stage for the orally administered antifungal azoles (24, 25). It can be administered both orally and topically and has a range of activity including infections due to *Histoplasma capsulatum* and *Blastomyces dermatitidis* for which it is often used in nonimmunocompromised patients. It is also active against mucosal candidiasis and a variety of cutaneous mycosis, including dermatophyte infections, pityriasis versicolor and cutaneous candidiasis. It is not indicated for treatment of aspergillosis or systemic infections caused by yeasts. The triazoles such as Fluconazole, Itraconazole have become the standard for the azoles and have replaced amphotericin B for managing certain forms of systemic mycosis. Fluconazole in new routinely used to treat candidemia in non-neutropenic host and is gaining acceptance for use in cryptococcosis and selected forms of coccidiomycosis. Itraconazole has proven to be effective for histoplasmosis, blastomycosis, sporotrichosis, coccidioidomycosis, consolidation treatment for cryptococcosis and certain and forms of aspergillosis. Fluconazole can be administered either orally or intravenously. Clinical isolates from diabetic patients had moderate resistance to fluconazole (FCZ). The lower sensitivity of Iranian isolates from Diabetes mellitus (DM) patients and their increased MIC patterns of antifungal agents may be related to the geography of the subject population, the environment of the lesion and microbial flora that exist in the lesions (26). The licensed formulation for Itraconazole is oral but, an intravenous formulation is under study and could be a significant addition directed at bioavailability problems relating to absorption of the oral formulation (25, 27). Side effect are not as common with the azoles as with amphotericin B, but life-threatening liver toxicity can be arise with long-term use liver toxicity noted with ketoconazole has been problematic with the triazole. Other side effects include nausea and vomiting. Drug interactions are a potential problem between azoles and other drug classes and include cyclosporine, certain antihistamines, anticoagulants and antiseizure, oral hypoglycemic and other medications that are metabolized via similar pathways in the liver (27).

Antimetabolites agent

In contrast to the situation with antibacterial agents, few antimetabolites are available for use against fungi. The best example is 5-fluorocytosine, a fluorinated analog of cytosine. It inhibits both DNA and RNA synthesis via intracytoplasmic conversion to 5-fluororacil. The latter is converted to two active nucleotides: 5-fluorouridine triphosphate, which inhibits RNA processing and 5-fluorodeoxyuridine monophosphate, which inhibits thymidylate synthase and hence the formation of the deoxythymidine triphosphate needed for DNA synthesis. As with other antimetabolites, the emergence of drug resistance is a problem. Therefor 5-fluorocytosine is seldom used alone. In combination with amphotericin B it remains the treatment of choice for cryptococcal meningitis is and effective against a number of other mycosis, including some caused by the dematiaceous

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fungi and perhaps even by *Candida albicans*(28-30).

Other antifungal agents

Griseofulvin is an antifungal antibiotic produced by *Penicillium griseofulvum*. It is active *in vitro* against most dermatophytes and has been the drug of choice for chronic infections caused by these fungi (e.g. nail infections with *Trichophyton rubrum*) since it is orally administered and presumably incorporated into actively growing tissue. It is still used in such instance but is being challenged by some of the newer azole antifungal agents (31). The drug inhibits mitosis and nucleic acid synthesis in fungi but has no effect against yeasts or other fungi. Griseofulvin is usually well tolerated. Adverse effects include headache, gastrointestinal disturbance and less commonly, urticarial, diarrhea and photosensitivity. The drug should be avoided during pregnancy and in patients with liver disease (32).

Potassium iodide given orally as a saturated suspension is uniquely used to treat cutaneous and lymphocutaneous sporotrichosis. This compound, interestingly is not active against *sporothrix schenckii in vitro*, it appears to act by enhancing the transepidermal elimination process in the infected host (5). Two other classes of antifungal agents represent new addition to topical treatment of the dermatomycosis in Europe. Two allylamines (naftifine, terbinafine) inhibit ergosterol synthesis at the level of squalene epoxidase; one morpholine derivative (amorolfine) inhibits at a subsequent step ergosterol pathway (33) (34).

Future agents

Powerful historical precedents support the use of antibody-based therapies to treat infectious diseases (35). However although still very early stages of development, newer approaches to the treatment of fungal infections will likely include the consideration of the host immune system and the interplay of drugs and host immunomodulators. Immunomodulators the therapies can be categorized as either pathogen specific or pathogen nonspecific (36). Pathogen-specific immunomodulators include antibody reagents and vaccines whereas cytokines, antimicrobial peptides and probiotics are considered pathogen nonspecific immunomodulators(37). Studies have shown immune sera to be protective in animal models of systemic candidiasis .Combination therapies using antifungal antibiotics with immunomodulators to treat invasive fungal disease are currently under investigation. To be of any clinical benefit, these regimens most improve efficacy without producing unacceptable side effects (36-39). The immunodominant fungal antigen heat shock protein 90 (HSP90), expressed on cell surface of yeasts and certain malignant cells, has been investigated as a potential target for antibody therapy (40, 41).

Mycograb® (Neutec pharma, Antwerp, Belgium), a human recombinant monoclonal antibody against HSP90 was shown to have synergistic activity with amphotericin B *in vitro* against a broad spectrum of *Candida* species (42, 43). Mycograb® consist of an antigen-binding variable domain of heavy and light chains linked together to create a recombinant protein that can be expressed in *Escherichia coli*. The antifungal activity of this drug can be demonstrated using assays, such as minimal inhibitory concentration testing, used to assess conventional antifungal drugs (43, 44). Other new antifungal agent under study include naturally derived molecules with antifungal properties, such as the antifungal protein (AFP) secreted by *Aspergillus giganteus*. AFP is a small (94 amino acids) positively charged amphipathic protein that exert no cytotoxic or immunogenic effect on mammalian cell, but interferes with the physiological properties and synthesis of the fungal cell wall leading to fungal cell death(45, 46). Recently, Zumbuehl et al, reported that a

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new dextran-based hydrogel containing amphotericin B Prevented fungal infections for at least 53 days when implanted in mice. The history antifungal agents continues to evolve and no doubt will produce novel agents that, it is hoped will target the organism as well as the host immunity (47).

Conclusion

Progress has been in the development of new antifungal compounds or analogs of existing drugs with broad spectrum of activity, more favorable pharmacokinetic profiles or better bioavailability. However, the development of more promising approaches as antifungal compounds with broader antifungal activity and fungal-specific mechanisms of action are a high priority.

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