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AN OVERVIEW OF: ANTIFUNGAL DRUGS

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ABSTRACT
We evaluated the registered antifungal medications and outlined their methods of action, pharmacological characteristics, and susceptibility to certain fungus. Approved antimycotics can inhibit 1,3-β-d-glucan synthase, lanosterol 14-αdemethylase, protein and deoxyribonucleic acid production, or sequester ergosterol. Their most serious side effects are hepatotoxicity, nephrotoxicity, and myelotoxicity. Echinocandins have essentially no drug-drug interactions, while triazoles have the most. Antifungal resistance can be established in most infections by drug target overexpression, efflux pump activation, and amino acid substitution. Additionally reviewed are the investigational antifungal medications undergoing clinical studies. The most promising new antifungal treatments are siderophores used in the Trojan horse technique or siderophore production enzyme inhibitors.

KEYWORDS: *invasive fungal infections, resistance, siderophores, triazoles, echinocandins, flucytosine, amphotericin B, and antifungal medications.*

INTRODUCTION

When Antifungal medications are used to treat infections caused by fungi, which can affect various parts of the body, including the skin, nails, respiratory system, and internal organs. Fungal infections range from mild conditions like athlete's foot to more severe systemic infections, especially in immunocompromised individuals. of action of many antifungal agents. 2,3 Fungal infections pose a continuous and serious threat to human health and life.1 These fungal infections in humans can be classified into (a) Allergic reactions to fungal proteins,
(b) Toxic reactions to toxins present in certain fungi and (c) Infections (mycoses).

Healthy individuals are susceptible to a host of superficial, cutaneous, subcutaneous and in certain instances, systemic infections that cause a variety of conditions ranging from Athletes foot and nail infections to severe life-threatening disseminated disease (e.g., histoplasmosis). 5 Many fungal infections are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections). 6 The incidence of mucormycosis may exceed 900,000 cases per year after the inclusion of Indian data estimates. 7 Furthermore, these infections are associated with high mortality rates. The epidemiology of invasive fungal infections usually focuses on specific areas. The lack of available global data leads to a broad range of mortality rates, 8 Typically a long period of 8 to 10 .10 Even though our modern healthcare is able to treat previously life-ending diseases, this often comes at the cost of immunosuppression. 9 Aspergillus and Candida spp. account for the majority of documented infections. The development of new antifungal drugs has been constantly required in the clinical therapy. 18

Aspergillus Niger
Aspergillus niger Van Tieghem causes a disease called black mould. The Aspergilli are a large and diverse genus. . The epidemiology of invasive aspergillosis indicates an increasing number of infections in immunosuppressed patients/individuals undergoing transplantation of bone marrow, hematopoietic stem cells, or organ transplantations, and those receiving intensive chemotherapy or other immunosuppressive treatment.

Mechanism of Action :- This review Describes the targets and mechanisms of action of all Classes of antifungal agents in clinical use or with Clinical potential. 13,14 Antifungal drugs target fungal infections by disrupting the structure or function of key components in fungal cells. Here is an overview of the main classes of antifungal drugs and their mechanisms of action:

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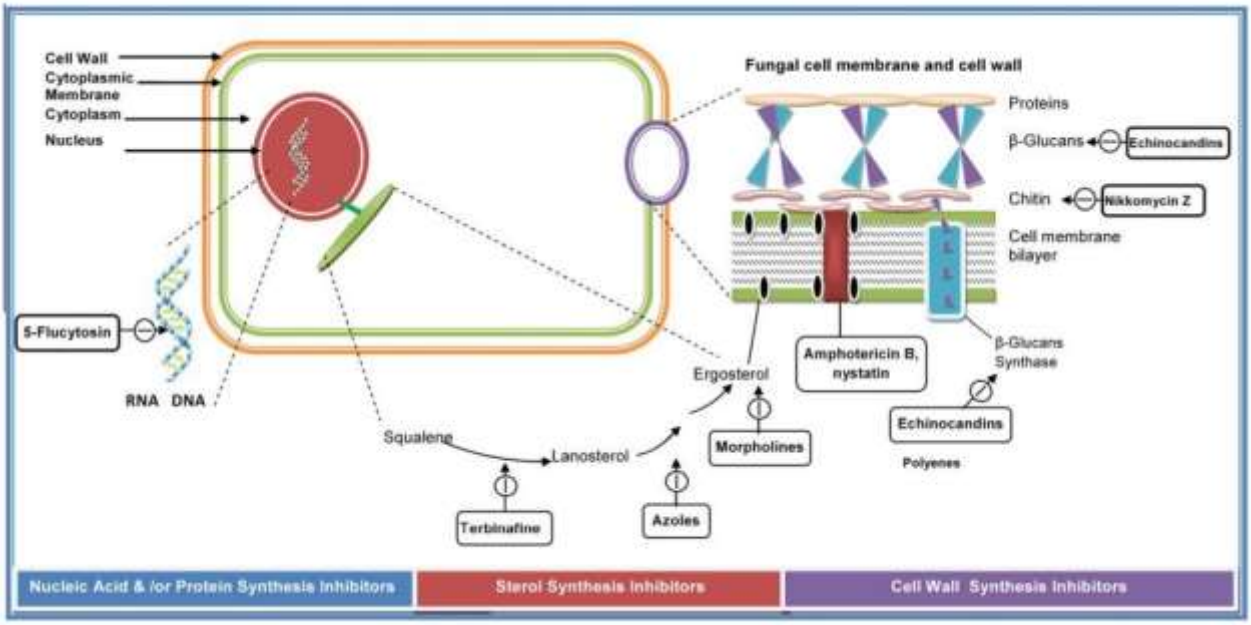

Fig. Targets for Antifungal Therapy

1. Polyenes (e.g., Amphotericin B, Nystatin)

Target: Ergosterol in fungal cell membranes.

Mechanism: These drugs bind to ergosterol, a key component of the fungal cell membrane, forming pores. This leads to leakage of essential ions (K^+, Na^+) and molecules, causing cell death.

2. Binding to Ergosterol

Target: Fungal cell membrane.

Drugs: Polyenes (e.g., amphotericin B, nystatin): Bind directly to ergosterol, forming pores in the membrane.

Effect: Leakage of intracellular ions and molecules, causing cell death.

Selective Toxicity: Humans have cholesterol instead of ergosterol, reducing drug effects on human cells.

3. Inhibition of Cell Wall Synthesis Target: Fungal cell wall.

Drugs: Echinocandins (e.g., caspofungin, micafungin): Inhibit β-1,3-glucan synthase, a critical enzyme for fungal cell wall glucan synthesis.

Effect: Weakening of the fungal cell wall, leading to osmotic instability and lysis

4. Inhibition of DNA/RNA Synthesis Target: Nucleic acid synthesis.

Drugs: Flucytosine (5-FC): A prodrug converted into 5-fluorouracil inside fungal cells, which inhibits thymidylate synthase and disrupts DNA and RNA synthesis.

Effect: Impaired fungal replication and protein synthesis.

5. Disruption of Microtubule Function Target: Fungal mitotic spindle.

Drugs: Griseofulvin: Binds to fungal tubulin, inhibiting mitosis.

Effect: Prevention of fungal cell division.

Tolnaftate: Mechanism: Inhibits squalene epoxidase, similar to allylamines.

Effect: Impaired ergosterol synthesis and membrane function.

Pharmacology and Toxicity of Antifungal Agents

Three lipidic formulations are commercially available: AMB lipid complex (ABLC), liposomal AMB (LAMB), and AMB colloidal dispersion (ABCD). 33

Generally, triazoles are well tolerated. The most common serious side effect, hepatotoxicity, occurs most often with VOR (in 31% cases). High protein binding and negligible metabolism by CYP450 are common among them; on the other hand, their half-life and degradation processes are different. Echinocandins have few known drug–drug interactions because of their reduced substrate potential to CYP450 enzymes. 20

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Here's an overview of the pharmacology and toxicity of antifungal agents:

Classes of Antifungal Agents

1. Polyenes: Amphotericin B, Nystatin
2. Azoles: Fluconazole, Itraconazole, Voriconazole, Posaconazole
3. Echinocandins: Caspofungin, Micafungin, Anidulafungin
4. Allylamines: Terbinafine
5. Flucytosine: 5-Fluorocytosine Pharmacology of Antifungal Agents*i

1. Mechanism of Action:
   - Azoles: Inhibit lanosterol 14α-demethylase, disrupting ergosterol synthesis.
   - Echinocandins: Inhibit β-glucan synthase, disrupting fungal cell wall synthesis.
   - Flucytosine: Converted to 5-fluorouracil, inhibiting DNA synthesis.
2. Pharmacokinetics:
   - Absorption: Variable, depending on agent and formulation.
   - Distribution: Generally distribute well into tissues, but may have limited penetration into certain sites (e.g., CSF).
   - Metabolism: Metabolized by liver enzymes, with some agents undergoing renal excretion.
   - Elimination: Half-lives vary, but generally range from several hours to several days.

Toxicity of Antifungal Agents

1. Common Toxicities:
   - Polyenes: Nephrotoxicity, infusion-related reactions.
   - Azoles: Hepatotoxicity, QT interval prolongation.
   - Echinocandins: Hepatotoxicity, infusion-related reactions.
   - Allylamines: Hepatotoxicity, gastrointestinal disturbances.
2. Less Common Toxicities:
   - Polyenes: Anaphylaxis, cardiac dysfunction.
   - Azoles: Seizures, Stevens-Johnson syndrome.
   - Echinocandins: Anaphylaxis, Stevens-Johnson syndrome.
   - Allylamines: Seizures, peripheral neuropathy.
   - Flucytosine: Pulmonary toxicity, neurological disturbances.

Monitoring and Management of Toxicity.

1. Monitoring:
   - Regular laboratory tests (e.g., liver function tests, complete blood counts).
   - Clinical monitoring for signs of toxicity (e.g., infusion-related reactions, hepatotoxicity).
2. Management:
   - Dose adjustment or discontinuation of the antifungal agent
   - Treatment of specific toxicities (e.g., hepatotoxicity with N-acetylcysteine).

It's essential to note that this is a general overview, and specific antifungal agents may have unique pharmacological and toxicological profiles. Always consult the latest clinical guidelines and prescribing information for specific agents.

Drugs :- Azoles

The azole drug These are synthetically derived antifungal agents, both used orally and topically. They are used for treating a large number of infections caused by dermatophytes, Candida, other fungi involved in deep mycosis, Nocardia, some gram-positive and anaerobic bacteria, e.g., Staphylococcus aureus, Enterococcus faecalis, Bacteroides fragilis and Leishmania.

Ketoconazole (KTZ) :- Ketoconazole is an antifungal drug that belongs to the imidazole class of azole antifungals. It has been widely used for systemic and topical fungal infections, though its systemic use has declined due to safety concerns. Here are the key aspects of ketoconazole. It can also be administered orally.

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Pharmacokinetics
The oral absorption of KTZ is improved by gastric acidity because it is more soluble at lower pH. The half-life is short and varies from 1.5-6 hours.
Side Effects : In females, menstrual irregularities may occur. Hepatotoxicity is also a side effect but is rarely fatal. 19,20

Antibiotics :- 1. Polyenes
Amphotericin B :-
Amphotericin B is an antifungal medication, not an antibiotic (which targets bacteria). However, I can provide you with some key information about Amphotericin.Amphotericin B was isolated from S. Adverse side effects associated with amphotericin B are infusional toxicity, nephrotoxicity and low blood potassium. 22
Mechanism of action
1. Binding to Ergosterol:
Amphotericin B has a high affinity for ergosterol, a key component of fungal cell membranes.
Ergosterol is essential for maintaining the structure and function of fungal cell membranes, making it a critical target.
2. Formation of Membrane Pores:
After binding to ergosterol, amphotericin B aggregates and forms pores or channels in the fungal cell membrane.
These pores create openings that disrupt the membrane's integrity.
3. Leakage of Cellular Contents:
The pores allow the uncontrolled leakage of:
Essential ions like potassium (K^+) and magnesium (Mg^{2+}). Metabolites and other small molecules.
4. Fungal cell death The loss of ions and critical molecules causes irreversible damage to the fungal cell, leading to cell death.

2. **Echinochandins**
Caspofungin
Caspofungin was approved by FDA for the treatment of patients with IA. Caspofungin has potent in vitro inhibitory activity against Aspergillus spp. and moderate activity against some other moulds such as H. capsulatum, C. immitis and B. dermatitidis. It is also active against P. carinii and moderately against dematiaceous fungi. But it has no activity against C. neoformans, Trichosporon spp., Fusarium spp., S. schenckii, zygomycetes and hyalohyphomycetes. 24,25 Caspofungin has few significant interactions as it is neither a substrate nor an inhibitor of the cytochrome P-450 system.

Side Effects
Caspofungin has few side effects, consisting mainly of headache, fever, nausea, rash, phlebitis at the site of infusion and reversible elevation of hepatic enzyme levels. 23

Heterocyclic Benzofuran
Griseofulvin
Griseofulvin is a narrow-spectrum antifungal agent isolated from cultures of Penicillium griseofulvum, and is active against dermatophytes, including Epidermophyton, Trichophyton, Microsporum, but not against fungi causing deep mycosis.

Mechanism of Action
Griseofulvin is an antifungal medication used to treat dermatophyte infections of the skin, hair, and nails. Its mechanism of action involves:

Inhibition of fungal mitosis: Griseofulvin disrupts fungal cell division by binding to microtubules, which are essential for mitotic spindle formation. This interference prevents the proper separation of chromosomes during mitosis, effectively halting fungal cell replication.

Deposition in keratinized tissues: Griseofulvin becomes concentrated in keratin precursor cells of the skin, hair, and nails. This keratin binding makes the tissue resistant to fungal invasion, helping eliminate the infection as the tissue regenerates and the infected keratin is replaced.

By targeting the fungal microtubules and localizing in keratin-rich areas, griseofulvin achieves both systemic and localized antifungal effects.

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Pharmacokinetics

1. Absorption

Griseofulvin is poorly water-soluble, and its absorption from the gastrointestinal (GI) tract is variable.

Enhanced absorption: Absorption is significantly improved when taken with highfat meals or in the micronized or ultramicronized formulations.

Peak plasma concentrations are reached approximately 4–6 hours after ingestion.

2. Distribution:

Griseofulvin is distributed widely throughout the body but accumulates primarily in keratinized tissues, such as skin, hair, and nails.

This selective deposition in keratinized tissues makes it effective against dermatophyte infections.

3. Metabolism:

Griseofulvin is metabolized in the liver, mainly via oxidation and demethylation.

The primary metabolite is 6-desmethylgriseofulvin, which has minimal antifungal activity. 4. Elimination:

The elimination half-life is approximately 9–24 hours, depending on the formulation and patient factors.

5. Bioavailability:

The bioavailability of griseofulvin is influenced by the particle size of the formulation:

Micronized formulation: About 25–70% bioavailability.

Ultramicronized formulation: Better bioavailability compared to micronized, requiring smaller doses for the same therapeutic effect.

Side Effects :-

Allergic reactions (rashes and fever) may occur. The drug is contraindicated in pregnant women. 26,27

3. Allylamines

Terbinafine

Terbinafine is an allylamine that has been available in the United States since May 1996. and other filamentous fungi but has variable activity against yeasts. Terbinafine has been shown to be fungicidal against dermatophytes, Sporothrix schenckii, dimorphic fungi, Scopulariopsis brevicaulis and Herdersonula and Acremonium species.49 Amorolfine can be used only for topical treatment of superficial mycoses, and neither of its targets has attracted recent research interest.

CONCLUSION

Fungal infections pose a continuous and serious threat to human health and life in recent years their has been an increased use of antifungal agents and has resulted in the development of resistance and toxicity, low efficacy rates. Antifungal drugs are essential for treating fungal infections, ranging from mild to life-threatening. Key drug classes like azoles, polyenes, echinocandins, and allylamines target fungal cells while minimizing harm to humans. Challenges include resistance, toxicity, and limited options. Advances in research aim to develop safer, more effective treatments and combat resistance. With rising fungal infections, improving antifungal therapies is crucial for global health.

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