Antifungal Drugs

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Introduction:

Superficial fungal infections occur much more frequently than system fungal infections.

The superficial mycoses are caused by two groups of organisms:-

1. ***Candida* species**
2. **Dermatophytes**

Superficial infection with **dermatopytes** is more common than superficial **candidiasis**. Candidal infections usually occur in mucous membranes or moist skin. However, candidal chronic infections may occur in scalp, skin, and nails. Dermatophytoses are generally confined to the skin, hair, and nails.

Systemic mycoses can be classified into two types:-

1. **Opportunistic infections**
2. **Non-opportunistic infections**

- The **opportunistic** mycoses, e.g. candidiasis, aspergillosis, cryptococcosis, mucormycosis, occur primarily in debilitated or immunocompromised host. While, **non-opportunistic** infections may occur in any subject; these infections are relatively uncommon and include sporotrichosis, blastomycosis, histoplasmosis, and coccidiodomycosis.
- These infections often pose a therapeutic problem because of their resistance to drugs, consequently requiring a long duration with high dose therapy with drugs that often exhibit high toxicities.

- Fungi may be classified as
  - Yeasts
  - Moulds
- Yeasts: Blastomyces, candida, histoplasma, coccidioides, cryptococcus.
- Moulds: Aspergillus spp. Dermatophytes, mucor
- Clinically classified as:
  - Superficial mycosis
  - Deep (systemic) mycosis

- Systemic fungal infections:
  - Systemic candidiasis: RTI with progressive dimunition
  - Cryptococcal meningitis, endocarditis
  - Rhinocerebral mucormycosis
  - Pulmonary aspergillosis
  - Blastomycosis (pneumonitis, with dissemination)
  - Histoplasmosis(cough , fever, multiple pneumonic infiltrates)
  - Coccidiodomycosis
  - Pnemocystis carinii pneumonia

Antifungal Drugs

The antifungal drugs are classified into two main groups:-

1- Drugs used to treat superficial mycoses (fungal infections)

A. Polyene antibiotics (e.g. nystatin and amphotericin B)
B. Imidazoles (e.g. ketoconazole, clotrimazole, miconazole, and econazole).
C. Others (e.g. griseo fulvin, flucytosine).

2- Drugs used to treat systemic mycoses

A. Amphotericin B
B. Flucytosine
C. Ketoconazole
D. Miconazole

Classification based on mechanism of action

1. Fungal cell wall synthesis inhibition: Caspofungin.
2. Bind to fungal cell membrane ergosterol: Amphotercin–B, Nystatin.
3. Inhibition of ergosterol + lanosterol synthesis: Terbinafine, Naftifine, Butenafine.
4. Inhibition of ergosterol synthesis: Azoles
5. Inhibition of nucleic acid synthesis: 5–Flucytosine.
6. Disruption of mitotic spindle and inhibition of fungal mitosis: Griseofulvin.
7. Miscellaneous:
   - Ciclopirox, Tolnaftate, Haloprogin, Undecylenic acid, Topical azoles.

Classification based on structure

- **ANTIBIOTICS**

  Polyene: Amphotericin, nystatin, hamycin

  Hetrocyclic benzofuran: griseofulvin

- **ANTIMETABOLITE :** Flucytosine

- **AZOLES**

  Imidazoles: Ketoconazole, clotrimazole, oxiconazole, miconazole,

  Triazoles: Fluconazole, itraconazole, voriconazole,

Classification based on structure

- **ALLYLAMINES**
  - Terbinafine, butenafine
- **ECHINOCANDINS**
  - Caspofungin, anidulafungin, micafungin
- **OTHER TOPICAL AGENTS**
  - Tolnaftate, Undecyclinic acid, benzoic acid

❑ POLYENE ANTIBIOTICS

❖ Nystatin

- Nystatin derived from *Streptomyces* cultures from the soil of Virginia and its name derived from the **New York State** Department of Health that was responsible for its culture.
- It is used topically for the treatment yeast-like fungi such as *Candida albicans*, also for vaginal infections.
- It is too toxic to be used systemically.

❖ Amphotericin

- Amphotericin B is a polyene compound that remains **the drug of choice for most serious systemic fungal infections**.

- It has serious toxic effects, primarily **nephrotoxicity**.

- It must be given intravenously; in meningitis due to fungal infection; it has to be given intrathecally to achieve adequate concentration in the CSF.

PHARMACOLOGY OF AMPHOTERICIN B

Chemistry

-**Amphotericin B** is a polyene antibiotic (polyene: containing many double bonds)

Mechanism of action

-Binding to ergosterol present in the membranes of fungal cells

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Formation of "pores" in the membrane

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Leaking of small molecules (mainly K+) from the cells

-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.

IMIDAZOLES

The imidazole antifungal agents constitute members which are used for superficial and systemic infections like ketoconazole, and to a lesser extent miconazole (rarely used systemic infections because of high toxicity); and clotrimazole and econazole are used for superficial infections and for topical application only.

The imidazole agents are useful for both dermatophytic and candidal infections.

Ketoconazole

Ketoconazole is the **only** imidazole antifungal drug that can be administered by mouth for treatment of superficial mycoses; it is active against a variety of fungal infections, dermatophytic infections and candidiasis of the skin, mouth, and vagina. Its oral absorption is variable, and only partially excreted in the urine.

- It carries a potential for **hepatic toxicity**; therefore, a regular assessment of hepatic function should be made. Because it blocks steroid synthesis,

- **it is useful in Cushing syndrome**, and may lead to hypoadrenalism and reduction in testosterone levels (**antiandrogenic activity**).
- It follows that because of the serious toxicity associated with its systemic use, oral ketoconazole is reserved for fungal infections that have failed to respond to topical agents like clotrimazole and miconazole.
- A topical preparation of ketoconazole is now available but its use is approved only for dermatophytic infections but not for candidiasis.

Clotrimazole

is a synthetic imidazole derivative that is topically active against dermatophytic infections and candidiasis of the skin, mouth and vagina.

Miconazole:

Miconazole is an imidazole antifungal agent available for topical and systemic administration. Because of high toxicity, the drug rarely used systemically; thus, it is a drug of first choice for dermatophytic infections, and cutaneous and vaginal candidiasis.

Econazole:

Econazole is an imidazole antifungal agent applied topically only. The drug is effective in *Tinea* infection and for superficial candidiasis.

PHARMACOLOGY OF ANTIFUNGAL AZOLES

Chemistry

-Imidazole derivatives: **ketoconazole**, miconazole, econazole, clotrimazole

-Triazole derivatives: **itraconazole, fluconazole**.

Mechanism of action

-Inhibition of sterol 14-alpha-demethylase, a cytochrome P450-dependent enzyme (relative selectivity occurs because the affinity for mammalian P450 isozymes is less than that for the fungal isozyme)

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blockade of the synthesis of ergosterol in fungal cell membranes

-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.

OTHERS

Griseofulvin

Griseofulvin is an antibiotic, isolated from *Penicillium griseofulvin* in 1939, which is active when given orally but not topically.

- Its only use is in the systemic treatment of dermatophytosis. The absorbed drug has an affinity for diseased skin and is deposited there, bound to keratin, making keratin resistant to fungal growth. Thus, new growth of hair or nails is free of infection. Therefore, it must be administered for 2-6 weeks for skin and hair infections. It is a **hepatic enzyme inducer**.

Flucytosine

Flucytosine is available for **oral or parenteral use**. It is mainly used in a synergistic combination with amphotericin against *Cryptococcus neoformans*. High plasma levels that often occur with renal impairment are associated with **bone marrow toxicity**, and monitoring of plasma concentration is therefore advised.

THANK YOU