Antifungal Agents

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Introduction

- Since fungi are eukaryotic, antibacterial agents are useless in eradicating mycoses.
- The first antibiotics that could inhibit eukaryotic fungal pathogens with out having a similar effect on the eukaryotic human host cells become available in 1959.
- Before that time, disseminated systemic infections by *coccidioides* and cryptococcus were usually fatal.
- Antibiotics called *Polyenes* and *azoles* are now used with reasonable success for treating fungal infection, depending on the specific disease.

7.1. Polyenes

- The most therapeutically valuable of the *polyenes* are those that bind with ergosterol, the sterol in fungal membranes, creating membrane pores and causing Leakage of cell metabolites.
- Human cells contain cholesterol instead of ergosterol and are there fore not as susceptible as fungi to these agents.
- The sterols in human cells, however, are some what affected by the pollyenes.

Polynes cont'd…

- Polyenes are among the few antimicrobials available for the treatment of
    - *cryptococcosis,*
    - *coccidiodomycosis,*
    - *aspergillosis,*
    - *mycormycosis,*
    - *candidiasis*
    - other potentially fatal systemic fungal infections
- amphoteriain B,. and Nystalin the drug in polyene group

7.2. Azoles

- The azoles are another group of synthetic compounds that interfere with the cell membrane of fungi.
- Unlike the polyenes, these compounds inhibit the synthesis of ergosterol.
- One group of azoles, the imidazoles, is effective broad spectrum antifungal drugs with few or no serious side effects.
- But there are other drugs in this group, such as clotrimazole, miconazole and ketoconazole.

Azoles cont'd…

- Another group of azoles are the triazole derivatives,
- It includes fluconazole and itraconazole
- These drugs have fewer side effects than the imidazoles for
- *Effective against cryptococcus* and oral candida infections in AIDS patients e.g. Fluconzole

Summary of the commonly used Anti fungal drugs

Amphotericin B

- Is a polyene anti fungal agent administered intravenously (IV)
- Causes nephrotoxicity
- Is the drug of choice in most life – threatening fungal infections

5-Fluors cytosine (5-Fc, flucytosine)

- Is an antimetabolic that is administered orally
- Is used primarily incombination with amphotericin B in the treatment of cryptococcal meningitis or alone at high strength to irrigate the bladder in the treatment of yeast infections.
- Some fungal infections develop a resistance to the drug.

Miconazode

- Is an imidazole requiring IV administration and exhibiting greater toxicity than ketoconzole
- Is used topically for mucocutaneous infections
- **Ketoconazole**
- Is an orally administered imidazole
- Can be used in non life- threatening systemic fungal infections and chronic mucocutaneous candidiasis
- It may be used in many other cutaneous infections

Ketoconazol cont’d

- It is effective against *Aspergillus*
- It is used in AIDS patients to reduce recurring fungal infections such as *Cryptococcus*
- Is administered orally to treat mucoctuaneous infections

Features of Antifungal Agents

Agent	Mechanism of Action	Mechanism of Resistance	Route	Clinical Use
Polyenes				
Nystatin	Membrane disruption	Sterol modification	Topical	Most fungi
Amphotericin B	Membrane disruption	Sterol modification	Intravenous	Most fungi
Azoles				
Ketoconazole	Demethylase block of ergosterol synthesis	Active efflux, demethylase alteration, or overproduction[a]	Oral	*Candida, Cryptococcus,* dimorphic fungi[b]
Fluconazole	Demethylase block of ergosterol synthesis	Active efflux, demethylase alteration, or overproduction[a]	Oral, intravenous	*Candida, Cryptococcus,* dimorphic fungi
Itraconazole	Demethylase block of ergosterol synthesis	Active efflux, demethylase alteration, or overproduction[a]	Oral, intravenous	*Candida, Cryptococcus,* dimorphic fungi, invasive molds (*Aspergillus*)
Clotrimazole	Demethylase block of ergosterol synthesis	Unknown[c]	Topical	*Candida,* some other yeasts
Miconazole	Demethylase block of ergosterol synthesis	Unknown[c]	Topical	*Candida,* some other yeasts
Voriconazole	Demethylase block of ergosterol synthesis	Unknown[c]	Oral, intravenous	*Candida,* some other yeasts and molds
Allylamines				
Terbinafine	Squalene accumulation	?Active efflux	Oral	Dermatophytes, combined with azoles for *Candida, Aspergillus*
Naftifine	Squalene accumulation	Unknown	Topical	Dermatophytes

Adopted from Sherris Medical Microbiology