PHARMA

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الكُتّاب: ليث الخزاعلة و ميس سلمان

المدققين: ليث الخزاعلة

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Antifungal Drugs

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Color code

Slides
Doctor
Additional info
Important

Antifungal Drugs

Superficial fungal infections are among the common causes of infections affecting the female genital system

Fungal Infections:

1. **Superficial fungal infections:**

A. **Dermatomycosis: Caused by *Trichophyton*, *Microsporum* and *Epidermophyton* and affect skin, nails and hair.**

B. **Candidiasis: affect skin, mucous membranes**

Antifungal Drugs

- Systemic fungal infections = deep fungal infections

2. **Systemic fungal infections: affecting deeper tissues and organs.**

- **The incidence and severity have increased since 1970s because of:**

A. **Wide use of broad spectrum antibiotics.**

B. **Immunosuppression: AIDS, Drugs, Chemotherapy**

C. **Older population**

D. **Diabetes mellitus**

E. **Advances in surgery**

Amphotericin B

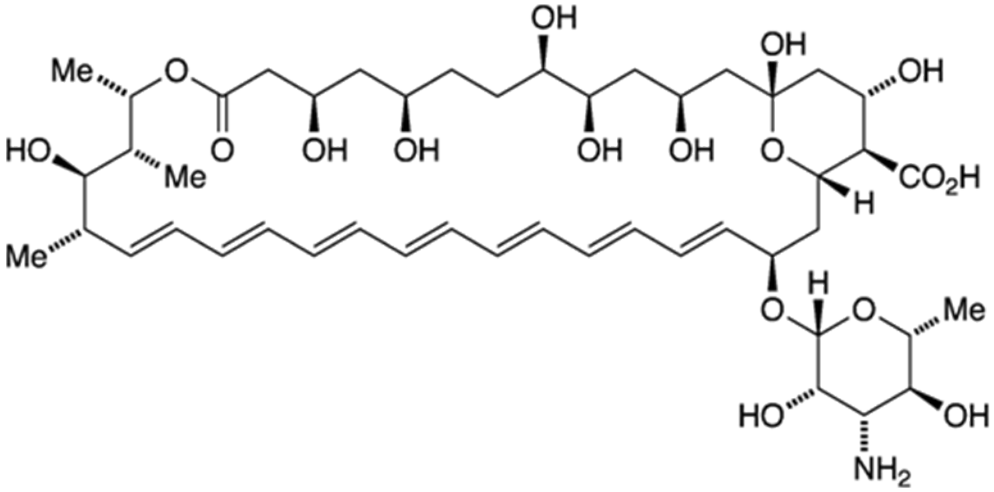
It's toxic and fungicidal, unlike most antifungals which are fungistatic.

- **A polyene macrolide antibiotic. It is a broad spectrum antifungal agent.**

Mechanism of Action:

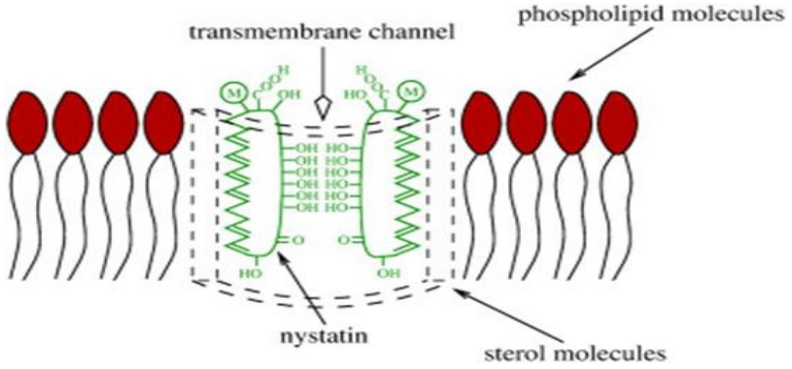
- **Binds ergosterol of fungal cell membrane → formation of amphotericin B associated-pores or transmembrane ion channels by the hydrophilic core of the molecule.**
- **Binding is relatively specific to fungi and the protozoan parasite Leishmania spp.**
- **The pore allows leakage of intracellular ions and macromolecules → cell death.**

The OH group is responsible for the hydrophilic part of this drug. So, in the structure, you can see that the hydrophobic part is bound on the sides and the hydrophilic part is balanced in the middle, forming a pore that increases membrane permeability. This allows important substances to leak out and harmful substances to enter, leading to cell death



Binding is relatively specific to fungi and the protozoan parasite Leishmania spp

Leishmania spp., because it forms the same type of pore in their cell membrane.



Amphotericin B

- **Resistance develops by modifying the sterol target → reduced affinity for the drug.**

Pharmacokinetics:

- **Poor absorption after oral administration.**
- **Can be used PO for fungal infections of GIT (lumen).**
- **It is complexed with deoxycholate as a suspension for slow IV infusion.**

Infusion, not injection. Infusion: slow and continuous. Injection: quick and direct.

Amphotericin B

- **Liposomal amphotericin B: packaging the drug in lipid delivery vehicles to reduce binding to human cell membranes → reduction of toxicity and permits use of larger doses.**
- **Highly protein bound (>90%)**
- **.**Crosses the BBB poorly, but penetration is improved when the meninges are inflamed. So, as inflammation decreases with treatment, penetration also decreases
- **t½ ~ 15 days long half life**

The dose is 1 mg/kg, meaning you take the amount based on your weight. But when it's bound to a liposome, the dose becomes 3 to 5 times more — around 3 mg/kg. This reduces binding to human cells, especially in the kidney, compared to deoxycholate

Amphotericin B

Adverse Effects:

A. Infusion-related toxicity:

- Fever, chills, muscle spasm, vomiting, headache and hypotension.
- Can be reduced by slowing the infusion rate.

Amphotericin B

B. Slower cumulative toxicity:

1. **Nephrotoxicity: common (> 80% of patients) and most serious, and constitute:**

a) **Reversible component: represents prerenal failure leading to renal tubular injury.**

Prevent by hydration

Amphotericin B

b) Irreversible component results from prolonged administration (> 4 gram cumulative dose): impaired renal concentrating ability, renal tubular acidosis and severe potassium, sodium and magnesium wasting.
c) Elevation of urea and creatinine.

Amphotericin B

2. **Anemia due to reduced erythropoietin production.**
3. **Others: Hepatic dysfunction, thrombocytopenia, anaphylaxis.**
4. **Seizures and chemical arachnoiditis after intrathecal therapy.**

Anaphylaxis occurs if the patient had previous exposure to Amphotericin B.

We give intrathecal therapy because Amphotericin B has poor penetration through the blood-brain barrier.

Amphotericin B

Mucor affects diabetic patients, starting with the skin and spreading to deep tissues. Treatment involves antimicrobial therapy and surgical removal of the affected tissue.

Antifungal Activity:

- **Broad spectrum and fungicidal**
- **Clinically significant yeasts:** **both are cause fungal meningitis**

  Candida albicans, cryptococcus neoformans
- **Endemic mycosis: *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidiodes immitis.***
- **Pathogenic molds: *Aspergillus fumigatus, Mucor.***

Nystatin

- **Is similar but more toxic than amphotericin B and only used for fungal infections of the skin & mucous membranes, as creams, ointments suppositories.**

Nystatin is similar to Amphotericin B (a polyene macrolide). It cannot be used systemically due to higher toxicity, but it can be used topically. It is used as suppositories for patients with anal fungal infections.

Flucytosine

Candida albicans, cryptococcus neoformans

- **Pyrimidine analog.**
- **Given PO & as IV infusion.**
- **Narrow spectrum: effective against yeasts.**
- **It has a synergistic effect when combined with amphotericin B for cryptococcal meningitis due to enhanced penetration through amphotericin B damaged membranes.**

The combination of Flucytosine and Amphotericin B is used to treat cryptococcal meningitis and is considered the most effective combination. Why? Because it reduces the duration of treatment by half — for example, if the treatment usually takes four days, it will take only two. This is because Amphotericin B kills the outer membrane of Cryptococcus, which facilitates the entry of Flucytosine to perform its action. The combination is considered synergistic, meaning 1 + 1 > 2

Flucytosine

Mechanism of action:

- It is taken up by fungal cells via cytosine permease.
- It is converted intracellularly to 5-fluorouracil (an analog) and then to 5-FdUMP and FUTP in fungal cells, which inhibit DNA and RNA synthesis, respectively. Fungostatic
- Human cells are unable to convert the drug into its active metabolites.
- Resistance emerges rapidly during monotherapy, due to altered metabolism of the drug.

Flucytosine

Flucytosine, when combined with amphotericin B, forms a good and synergistic combination for treating cryptococcal meningitis

Pharmacokinetics:

- Well absorbed after oral administration (> 90%).
- Widely distributed throughout body fluids including CNS.
- 90% excreted unchanged by the kidney by glomerular filtration.
- t½ ~3-4 hours.
- Dose reduction is needed in renal dysfunction.

Flucytosine

A narrow therapeutic window can develop due to an overlap between therapeutic and toxic concentrations, or when both concentrations are close together. Even slight variability in the dose can lead to adverse reactions.

Adverse Effects:

- **It has a narrow therapeutic window: toxicity develops rapidly at high blood levels, with resistance developing rapidly at subtherapeutic levels.**
  If the dose is not enough, resistance may develop

1. **GIT disturbances: enterocolitis and hepatitis.**
2. **Bone marrow depression: anemia, neutropenia, thrombocytopenia most common.**

Monitoring is done through CBC. We also need to measure the drug's plasma or serum concentration to ensure it stays within the therapeutic window. Therapeutic monitoring involves measuring the plasma concentration of the drug in conjunction with the clinical picture

3. **Alopecia.**

Azole Antifungals

While azoles are mostly synthetic, amphotericin B is a natural compound. Flucytosine is considered semi-natural, as it is derived from cytosine with the addition of a fluorine atom.

Classification:

1. Imidazoles: Ketoconazole, Miconazole & Clotrimazole

Ketoconazole is the prototype azole, but it is the least used due to its high toxicity. It inhibits steroidogenesis, including the production of corticosteroids, androgens, and estrogens. However, it can still be used topically for superficial infections

1. Triazoles: Itraconazole, Fluconazole & Voriconazole

Fluconazole contains fluoride, which makes it more lipid-soluble and allows it to penetrate tissues more easily. It can be used to treat cryptococcal meningitis, although flucytosine is more effective

- There are broad spectrum synthetic fungistatic antifungal agents

Azole antifungals differ in their antifungal spectrum and order of development. Imidazoles appeared first, while triazoles are the most recent

Azole Antifungals

Antifungal Spectrum:

- **Many candida, *Cryptococcus neoformans*, the endemic mycoses (blastomycosis, coccidioidmycosis, histoplasmosis), and the dermatophytes.**
- **Itraconazole and voriconazole: *Aspergillus*, and amphotericin-resistant *Pseudallescheria boydii*.**

Infection with Pseudallescheria boydii happen in immunocompromised patients, it is sensitive to amphotericin B, but resistance may develop.

Azole Antifungals

Mechanism of Action:

- **Inhibition of fungal cytochrome P450 responsible for synthesis of ergosterol of cell membrane → alteration of membrane fluidity and thus, the activity of membrane-associated enzymes.**
- **The net effect is inhibition of replication and growth.** Fungostatic

- **They reduce the formation of amphotericin B binding sites.**

Azole Antifungals

- **Imidazoles also inhibit human P450, leading to a higher incidence of drug interactions and adverse effects.**

Fluconazole

- **Can be given PO (high oral availability) (because It rapidly crosses the membrane and absorbed)& IV.**
- **Reaches high concentration in CSF and ocular fluid.**
- **This allows us to treat fungal infections in the eye.** Remember that certain compartments in the body—such as the globe of the eye, the prostate, and abscesses—are difficult for antibiotics and antifungals to reach
- **Effective in most fungal meningitis (cryptococcal, coccidioidal) and candidemia.**
- It is not the drug of choice, but it is effective in most cases of fungal meningitis. Flucytosine is more effective and can reduce the duration of infection by two weeks
- **Useful in mucocutaneous candidiasis.**
- **No activity against aspergillus or other filamentous fungi.**

However, remember that voriconazole and itraconazole are active against *Aspergillus*

Fluconazole

- **Prophylactic use in bone marrow transplants & AIDS → emergence of resistance.**
- **Fungicidal concentrations can be achieved in vaginal tissue, saliva, skin & nails !!!.**

Drugs suitable for treating nail infections must concentrate in keratin.
Fluconazole has an affinity for the nails and epidermis

- **Excreted unchanged mostly in urine.**

Fluconazole

Adverse Effects:

- **Has the widest therapeutic index of azoles.**

1. **Nausea, headache, abdominal pain**
2. **Exfoliative skin lesions (Steven-Johnson syndrome) have been seen in AIDS patients**
3. **Hepatitis**
4. **Does not inhibit drug metabolism and steroidogenesis like ketoconazole → Less drug interactions.**

It is very important that if we decide to use conazoles for their effect, their impact on steroidogenesis will determine whether they can be used or not.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!