ANTIFUNGAL DRUGS

University Of Nairobi

Department Of Public Health, Pharmacology & Toxicology

JPT 341 Pharmacology &Toxicology

BVM 3RD Year Lecture Notes

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Lecture objectives

1. By the end of this lecture the students should be able;

   - ❖ To give major groups and specific examples of the antifungal drugs.
   - ❖ To describe the mechanisms of action antifungal drugs including their pharmacological effects.
   - ❖ To outline clinical applications the drugs vet medicine.

Lecture outline

- Introduction
- Classification of antifungal drugs
- Polyene Macrolides antifungals
- Imidazoles
- Fluorinated pyrimidine derivatives
- Benzofurans Derivatives
- Iodides
- Other antifungal drugs

Introduction

- Pathogenic fungi of animals and humans are generally filamentous molds or intracellular yeasts.

- The fungal cell wall contains chitin and polysaccharides making it rigid, and acts as a barrier to drug penetration.

- The cell membrane contains ergosterol, which influences the efficacy and the risk of drug resistance.

- Most antifungal agents are fungistatic with infection-clearance largely dependent on host response.

Classification of antifungal drugs

- **Based on chemical structures**: The classes include Polyene macrolides, Imidazoles, Fluorinated pyrimidines, Benzo-furans and Iodides

- **Based on their sites of action**: Either systemic or topical antifungal drugs.

- **Miscellaneous classifications**: Organic acids and their salts and other inorganic salts

Polyene Macrolides antifungals

- Polyene macrolides antifungals were isolated from various species of *Streptomyces*.

- Examples used in veterinary medicine include;
    - ❖ Amphotericin B,
    - ❖ Nystatin
    - ❖ Pimaricin (natamycin)

Mechanisms of polyene macrolides

- Polyene macrolides bind to sterols (ergosterol) in the cell membrane of susceptible fungi.

- This creates a transmembrane channel, changing membrane permeability and thus allowing leakage of intracellular components.

- In particular, amphotericin B binds to ergosterol in fungal membranes disrupting its function leading to K^+ ion efflux and H^+ ion influx.

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Mechanisms of polyene macrolides

- Consequently, internal acidification of fungal cell occurs and thus stopping enzymatic functions. Sugars and amino acids also leak from an arrested cell.

- For Natamycin, the binding to ergosterol in the plasma membrane, prevents ergosterol-dependent fusion of vacuoles, as well as membrane fusion and fission.

- This differs from the mechanism of amphotericin B, which alters fungal membrane permeability.

Spectrum of activity of polyene macrolides

- They have broad antifungal activity including filamentous fungi, saprophytic and pathogenic fungi.
- Amphotericin B is effective against Coccidiomycosis, histoplasmosis, candidiasis and blastomycosis.
- Nystatin is effective against candidiasis against, other yeasts and fungi.
- Pimaricin is effective against candidiasis, trichomoniasis, and mycotic keratitis (dermatophytes).

Indications and dose rates

- Amphotericin B is used for the treatment of systemic mycotic infections.

- Nystatin is indicated for the treatment of mucocutaneous or intestinal candidiasis.

- Pimaricin is used in therapeutic management of mycotic keratitis.

Adverse effects, toxicity and drug interactions

- Oral administration of nystatin can lead to anorexia and GIT disturbances

- Amphotericin B may cause nephrotoxicity after IV infusion. The drug may also cause anorexia, nausea, vomiting, hypersensitivity and drug fever.

- Rifampin may potentiate the amphotericin B activity.

- Amphotericin B should be contraindicated during therapy with aminoglycosides (nephrotoxicity)

Adverse effects, toxicity and drug interactions

- The drug should not administered with digitalis drugs (increased toxicity), and neuromuscular blocking drugs.

- It should be avoided when mineralocorticoids, thiazide diuretics, antineoplastic drugs, and cyclosporine have been used.

Imidazole antifungal drugs

- Imidazoles antifungals contains imidazole ring in their chemical structures.

- Some imidazoles also have antibacterial, antifungal, antiprotozoal, and anthelmintic activity.

- Examples of imidazole derivatives used as antifungals are; clotrimazole, miconazole, econazole, ketoconazole, itraconazole, and fluconazole.

Mode of action of imidazole antifungal drugs

- Imidazoles block the synthesis of ergosterol, the primary cell sterol of fungi thereby altering the cell membrane permeability of yeasts and fungi.

- They also impair enzymes required for fatty acid synthesis and also cause toxic concentrations of hydrogen peroxide to develop intracellularly due to changes in oxidative and peroxidative enzyme activities.

- This results in cell membrane and internal organelle disruption and cell death.

Activity spectrum and indications of imidazole antifungals

- Miconazole has a wide antifungal spectrum against most fungi and yeasts of veterinary interest.

- Ketoconazole is more effective against *C immitis* and some other yeasts and fungi.

- Itraconazole and fluconazole are active against dimorphic fungal organisms and dermatophytes.

- Clotrimazole and econazole are used for superficial mycoses (dermatophytosis and candidiasis);

Activity spectrum and indications of imidazole antifungals

- Fluconazole are indicated for tissues that are tough to penetrate.

- Both itraconazole and fluconazole may be used for the treatment of systemic aspergillosis and sporotrichosis infections.

- Thiabendazole is included in some ear preparations for treatment of yeast infections.

Adverse effects, toxicity and drug interactions

- Ketoconazole given orally may result in nausea, vomiting, and hepatic dysfunction, as well as altered testosterone and cortisol metabolism.

- Reproductive disorders related to ketoconazole administration may be seen in dogs.

- Voriconazole is associated with a number of adverse effects in humans, including vision disturbances.

Adverse effects, toxicity and drug interactions

- The imidazoles may be used concurrently with amphotericin B or 5-flucytosine to potentiate its antifungal activity.

- The absorption of the imidazoles, (except for that of fluconazole), is inhibited by concurrent administration of cimetidine, ranitidine, anticholinergic agents, or gastric antacids.

Adverse effects, toxicity and drug interactions

- The risk of hepatotoxicity is increased if ketoconazole and griseofulvin are administered together.

- Rifampin decreases the serum levels of active ketoconazole because of microsomal enzyme induction

Fluorinated pyrimidine derivatives

- This antifungal drug includes fluorinated pyrimidine cytosine analog that is related to fluorouracil.
- Example includes flucytosine (5-fluorocytosine)
- The drug was initially developed as an antineoplastic agent.

Mode of action of flucytosine

- Flucytosine is converted by cytosine deaminase in fungal cells to fluorouracil, which interferes with RNA and protein synthesis.

- Fluorouracil is metabolized to 5-fluorodeoxyuridylic acid, which inhibits thymidylate synthetase required for DNA synthesis.

- These effects eventually inhibits DNA synthesis and may cause fungal cell deaths.

Spectrum of activity, indications and dose rates

- Flucytosine is effective against *Cryptococcus neoformans*, *Candida albicans*, *Phialophora* and *Cladosporium* spps.

- The common indications for flucytosine are cryptococcal meningitis, used together with amphotericin B.

- General dosages are 25–50 mg/kg and 30–40 mg/kg, orally 4 times a day in dogs and cats, respectively.

Adverse effects, toxicity and interactions

- Flucytosine is toxic at high doses and leads to nausea, vomiting, and diarrhea.
- It causes reversible increased liver enzymes, anemia, neutropenia, thrombocytopenia).
- The renal effects of amphotericin B prolong elimination of flucytosine.
- If flucytosine is combined with immunosuppressive drugs, depression of bone marrow function is possible.

Benzofurans Derivatives

- Benzofuran derivative includes Griseofulvin which is fungistatic but is fungicidal for young active cells.

- Griseofulvin accumulates in the stratum corneum and is highly effective against the dermatophytes.

- Dermatophytes are resistant to griseofulvin *in vitro*.

Mode of action of griseofulvin

- Griseofulvin disrupts the mitotic spindle by interacting with the polymerized microtubules in susceptible dermatophytes.

- This results in the production of multinucleate fungal cells. The drug also acts by inhibiting nucleic acid synthesis and forms hyphal cell wall material.

- This results in distortion, irregular swelling, and spiral curling of the hyphae.

Spectrum of activity, indications and dose rates

- Griseofulvin is active against *Microsporum*, *Epidermophyton*, and *Trichophyton spp*.

- Indicated for infections in dogs, cats, calves, horses, and other domestic and exotic animal species.

- Dogs and cats the dose rate is 10-30 or 130mg/Kg orally single dose or divided twice or three times per day.

- Horses and cattle the dose rate is 5-10 mg/Kg orally.

Adverse effects, toxicity and drug interactions

- Adverse effects induced by griseofulvin but nausea, vomiting, diarrhea and hepatotoxicity may be seen.
- Griseofulvin is contraindicated in pregnant mares and queens because it is teratogenic.
- Lipids increase the GI absorption of griseofulvin.

Adverse effects, toxicity and drug interactions

- Barbiturates decrease absorption and antifungal activity of Griseofulvin.

- Griseofulvin is a microsomal enzyme inducer and promotes the biotransformation of concurrently administered drugs.

- The combined use of ketoconazole and griseofulvin may lead to hepatotoxicity

Iodide antifungals

- Sodium and potassium iodide are used to treat selected bacterial, actinomycete, and fungal infections with sodium iodide being preferred.

- Long term use at high levels leads to accumulation in the body and to iodinism.

- Sodium iodide has been used successfully to treat cutaneous and cutaneous/lymphadenitis forms of sporotrichosis.

Other antifungal drugs

- **Topical antifungal agents are** applied topically, either on the skin, in the ear or eye, or on mucous membranes to control superficial mycotic infections.

- ***Amorolfine*** is a morpholine derivative that may interfere with the synthesis of sterols essential for the functioning of fungal cell membranes. It is used to treat onychomycosis and dermatophytosis.

- Other topical agents include iodine, amordfine, terbinafine, cidopiroxolamine, tolnaflate and candicidin

Examples of topical antifungal agents

- ***Terbinafine*** is an allylamine antifungal agent available as a topical cream or as tablets. It decreases synthesis of ergosterol by inhibiting squalene epoxidase.

- Terbinafine iis used in the treatment of dermatophytes and yeasts. It is used in combination with other antifungal drugs to enhance its efficacy.

- ***Others are Organic acids***: undecylenic acid, caprylic and propionic acid as well as benzoic acid and salicylic acid.

References

- Veterinary Applied Pharmacology and Therapeutics
- Applied veterinary pharmacology and Therapeutics by *Jim E. Riviere and Mark G. Papich(Ed.)*. 9th Edition
- *DrugBank: http://www.drugbank.ca/drugs/*