Pharmacology Lec 9 Antifungal Agents Dr.Siham

ANTIFUNGAL AGENTS.

Griseofulvin.

Griseofulvin is actively taken up by growing dermatophytes(ringworm).

Mechanism of action.

It binds to microtubules to inhibit spindle formation and mitosis.

It is fungistatic for dermatophytes such as Microsporum spp. and Trichophyton spp.

Therapeutic uses.

Griseofulvin is used in dogs, cats, and horses for multifocal dermatophyte

infections.

Adverse effects.

Untoward effects are rare. Leucopenia and anemia may occur as

an idiosyncratic reaction in kittens.

Nystatin and Natamycin

Chemistry. Nystatin and natamycin are polyene antibiotics derived from Streptomyces spp.

Mechanism of action.

Nystatin and natamycin are fungicidal to yeast infections caused by Candida

spp. and Malassezia spp. They act by binding to erogsterol of the protoplast membrane of fungi to alter permeability and allow leakage of cell counts .

Therapeutic uses.

Nystatin and natamycin are too toxic for parenteral use. They are administered topically for yeast infections of the eye, ear, and skin, and

administered orally for treating mucosal yeast infections of the mouth and GI tract.

Nystatin is used as a feed additive in poultry to prevent crop mycosis and mycotic diarrhea.

Pharmacokinetics. Nystatin is not absorbed orally and is excreted in the feces.

Administration. Nystatin is administered orally every 6–8 hours for Candidal infections in dogs and cats.

Natamycin is used topically primarily for ocular mycotic infections and is

the drug of choice for treating fungal keratitis in horses.

Adverse effects. Adverse effects are rare since the drugs are not supposed to enter the systemic circulation. Occasional GI upset may be observed with high dose.

Azoles

Chemistry.

Ketoconazole, itraconazole, and fluconazole are imidazole antifungals for systemic use.

Other imidazoles used only topically for dermatophyte, Aspergillus

or yeast infections include miconazole and clotrimazole.

Mechanism of action.

The azoles inhibit the synthesis of ergosterol in fungal cytoplasmic membranes by blocking cytochrome P450 enzymes and increasing cellular permeability.

At high doses, mammalian steroid synthesis (corticosteroids and sex steroids

) is inhibited. Azoles are fungistatic for most pathogenic fungi causing systemic infections such as Blastomyces, Coccidioides, Cryptococcus, and Histoplasma spp.

They are also effective against candidiasis and griseofulvin-resistant dermatophytes.

Therapeutic uses.

Ketoconazole is used in dogs, cats, horses, and birds for systemic mycoses and for severe yeast infections.

It is also used in dogs and cats at high dosage for the treatment of hyper adrenocorticism.

Fluconazole and itraconazole have replaced ketoconazole in most treatment regimens for the systemic mycoses because of their longer t 1/2 , greater activity, and lower toxicity.

Clotrimazole and miconazole are used topically in the treatment of Candida , Aspergillus, and dermatophyte infections.

Adverse effects.

Anorexia, vomiting, and diarrhea may occur, especially in cats, treated with ketoconazole. Suppression of adrenal or gonadal steroids may also occur but the effects are transient at doses employed in antifungal therapy. Adverse effects are rare with fluconazole or itraconazole therapy, unless in patients with impaired renal function.

Amphotericin B

Mechanism of action.

Amphotericin B binds to ergosterol of fungal cell membranes to from pores

to form pores or channels, which result in leakage of cell contents.

It is fungicidal against most organisms causing systemic mycoses, including Aspergillus, Blastomyces, Coccidioides, Cryptococcus, and Histoplasma spp

Therapeutic uses.

Amphotericin B is used to treat systemic fungal infections in dogs ,cats ,horses , and birds. Combined therapy with ketoconazole, fluconazole,

itraconazole (to reduce toxicity), or flucytosine (for CNS, bone, or ocular infections) is common .

Adverse effects.

Renal toxicity is a serious side effect. Amphotericin B produces renal

vasoconstriction, decreased GFR, and damage to tubular epithelium. BUN

must be monitored weekly during therapy.

Flucytosine

Mechanism of action.

Flucytosine inhibits thymidylate synthase and DNA and RNA synthesis in susceptible fungi. It is fungicidal against Cryptococcus, Candida, and

Aspergillus spp.

Therapeutic uses.

Flucytosine is combined with amphotericin B for synergistic action in the treatment of Cryptococcosis (especially meningeal cryptococcosis) in

dogs and cats.

It is used alone in treating aspergillosis and candidiasis in psittacine

birds.

Adverse effects.

Toxicity is low. Mild GI disturbances and, more rarely, bone marrow suppression have been reported.

Terbinafine

Mechanism of action.

Terbinafine inhibits the synthesis of ergosterol—a component of fungal cell membranes. By blocking the enzyme squalene monooxygenase(squalene 2,3-epoxidase), terbinafine inhibits the conversion of squalene to sterols (especially ergosterol) and causes accumulation of squalene. Both these effects are thought to contribute to its antifungal action. Unlike azoles, terbinafine does not block cytochrome P450 enzymes. It is fungicidal against dermatophytes and fungistatic against yeast.

Therapeutic uses.

When administered orally (30 mg/kg/day) or topically, terbinafine is useful for treating dermatophytic infections in dogs and cats.

It is also useful for treating birds for systemic mycotic infections such as aspergillosis.

5. Adverse effects. Terbinafine appears to be well tolerated by animals.