POLYENE MACROLIDE

Antibiotics Amphotericin B

Example of polyene: (multiple double bond)

1. This includes amphotericin B
2. Nystatin
3. Pimaricin

Chemistry: they consist of macrolide containing a large lactone ring. The polyene contains many double bonds and represents the lipophilic portion of the molecule.the polyene compounds are in-stable in water and are unstable, thus, will rapidly decompose if exposed to sunlight.

Mode of action

Polyene macrolides bind with sterol portion of phospholipids comprising the fungal cell membrane. Amphotericin has a much high affinity for ***ergosterol*** than for cholesterol. This would cause a distortion in the cell membrane permeability and altered K^+/ H^+ exchange and K^+ and Mg^{2+} from the cell . this would cause cellular Metabolism to be disrupted .

Amphotericin C has Immunodulatory characteristics so the cell mediated immunity may be enhanced so may increase the ability of the patient to overcome the infection

SPECTRUM OF ACTIVITY

It is effective against major fungal pathogens like, *histoplasmosis, blastomycosis, (crytococcosis and coccidiomycosis)* and dessiminated sporotrichosis, *phycomycosis aspergillosis* and *candidiasis.*

It is also effective against coccidiodal meningitis

Resistance of Polyene of Amphotericin B

Incidence of Resistance had been documented primarily for candida

PHARMACOKINETICS

- Amphotericin is not water soluble and thus is not bioavailable after oral administration.
- It is 90% bound to lipoprotein and thus penetrates pleura, peritoneum, inflamed tissues, cerebrospinal fluid and aqueous humour.
- Primary method of elimination is biliary elimination and only 3% of the drug is eliminated in urine

Side Effects

- Nephrotoxicity is the major toxicity other side effect are
- Nausea
- Anorexia
- Thrombophlebitis
- Cardiac arrythrnias
- Hepatic dysfunction
- C.N.S signs

Three strategies to prevent amphotericin B Toxicity

1. First pretreatment with anti- histamines such as diphenhydramine, hydrocortisone sodium succinate 0.5mg / kg, 1.V
2. Pretreatment with sodium- containing fluids. This would prevent renal toxicity and associated renal aterial Vasoconstriction.
3. Administration of Amphotericin diluted in 5% dextrose with mannitol (0.5mg/kg) to maintain glomerular filtration rate and sodium bicarbonate at 1-2mg/kg to prevent cellular acidification defects more recently a specialized delivery system (in lipids) specialized to deliver the drug selectively to the site of the infection. The lyposomal carrier system (L-AMB)

IMIDAZOLE DERIVATIVES

The Imidazole or triazoles are also called azole derivatives,

Chemistry:- these drugs consist of five member ring with other aromatic rings attached via a carbon nitrogen bond. They are insoluble in water azoles

Examples of azole: ketaconazole, (the prototype) Miconzole, clotrimazole, thiabendazole

New drugs: fluconazole, itraconazole enilconazole, and terconazole.

Mode of action:

Ketoconazole has a mechanism of action similar to the amphotericin B that is interference with ergesterol. But the primary mechanism of action of other derivatives are to block its synthesis via inhibition of the fungal **cytochrome p-450** enzymes. Cell membrane fluid decreases and cell permeability increases resulting in fungistatic effect. And at higher doses or concentration they interfere with physiochemical intracellular process and thus, confer its fungicidal effect.

Therapeutic advantage of azoles

The imidazoles are also characterized by immunomodulatory effect which may facilitate the therapy.

This drugs possess long elimination half life of some members results to lag-time effect (e.g. itraconazole) thus, in a in a lag-time as steady-state concentration are achieved.

Spectrum of activity

The imidazoles are more selective in their cellular activity than amphotericin B. the imidazioles are effective against:

- Demartophytes

- Microsporum
- Trichophyton
- Yeast.

Dimorphic fungi (*blastomycosis, eumycetes, actinomyces and phycomyces*). In general the newer itraconazole and fluconazole is more effective against organisms than ketoconazole.

Pharmacokinetics

- Oral preparation is not too common.
- But oral absorption is dependent on pH of the GIT.
- Itraconazole and ketoconazole is enhanced by gastric acidity and should be administered with food.
- Peak concentration of itraconazole is between 1 to 5 hours in cats.
- Bioavailability may be 20% in dogs and 10% in cats.
- Distribution of imidazoles is up to 99% protein bound and the highest tissue level occur in liver, lung, and kidney.
- Those drugs have minimal penetration into the CSF.
- The half-life of drugs vary from 1- 4hours – in dogs for (ketoconazole) to 22 – 32 hours in humans for (Itracionazole) and 51 hours in the dog for (Itraconazole) and may range between 40 – 70 hours for (Itraconazole) in cats.

Therapeutic uses

Among the imidazoles itraconazole and fluconazole are being used consistently than other in systemic infections treatment.

Itraconazole is also used in humans in dermatiologic fungal disorders.

Side effects: *Cardiotoxicity, dermatitis, vasuclitis.*

Anti metabolites

Examples are 5-flucytosine (Flu; 5-fluorocytosine)

5-flucytosine (Flu; 5-fluorocytosine) it's a water soluble powder and originally developed as an anticancer drug.

Mode of Action

Flu interferes with DNA synthesis after conversion to 5-fluorouracil, a substitution compound that prevents synthesis in fungal cell**.** **The enzyme responsible for the conversion to 5-fluorouracil, a cytosine deaminase, is not present in mammalian cells. Fluorouracil undergoes additional metabolism before inhibiting thymidylate synthase and DNA synthesis.**

Spectrum of Activity - Could be sused in;

- *Cryptococcosis*
- *Candidiasis.*
- *Cladosporiosis*
- *Aspergillosis*
- *Chromomycosis*
- *Sporotrichosis*
- **Pharmacokinetics**
- Oral absorption is rapid
- Peak plasma concentration occurs in 1 to 2 hours
- Protein binding is minimal.
- Distribution is large.
- $t^1/_2$ is 3-6 hours.

- The drug is excreted unchanged in urine.
- Renal clearance is similar to that of creatinine.

Side Effects

Because Flu interferes with DNA synthesis, body systems composed rapidly dividing cells thus, cells of the erythropoetic centres to cause bone marrow – depression, anaemia, thrombocytopenia, (panycytopenia).

GIT toxicity, nausea, vomiting and diarrhea.

Skin – erythematous lesion, alopecicdermatitis.

SUPERFICIAL ANTIFUNGAL AGENTS

Grisseofulvin

Griseofulvin is produced from *Penicillium* species bacterium. The drug is insoluble in water.

Mechanism of action:

Griseofluvin enters fungi through an energy-dependent transportt system. Griseofluvin inhibits fungal mitosis by binding to the microtubules that form the mitotic spindle.

Spectrum of activity:

The spectrum of activity is limited to dermatophytes: *Microsporum, trichophyton, and Epidermophyton.*

Pharmacokinetics

- Griseofluvin is insoluble and oral absorption varies due to insolubility.
- The absorption of drug is increased in fats.
- Bioavailability of the drug of the ultramicrosize is at least 50% greater than that of the microsize.
- The drug penetrates the *stratum corneum.*

- The drug after administration is deposited or concentrated in the skin, nails, and hair.
- Skin infection require 4 to 6 weeks of therapy where as toe nails may require up to a year therapy.
- $t^1/_2$ is 24 hours in dog.
- The drug is metabolized by dealkylation in the liver.
- The rest of drug is excreted unchanged.

ANTIPROTOZOAN AGENTS

INSTRUCTIONAL OBJECTIVES

- List drugs used to treat trypanosomosis
- Drugs used to treat piroplasmosis prevalent in Nigeria.
- Have idea of mechanism of actions of drugs used, side effects, and Pharmacology.
- Vividly list other drugs used to treat giardiasis, cryptosporidiosis, toxoplasmosis.
- Therapuetic rational use in anticoccidials

Protozoal infections are common in tropical and sub tropical countries where sanitary conditions, hygiene practices, and control of the vectors of transmission are inadequate. Two types of infections caused by the major types of protozoa of veterinary importance are the haemoparasitic e. g. trypanosome, babesia, theileria, and the common enteric coccidian, toxoplasma and giardia.

ANTI TRYPANOSOMAL DRUGS:

Diamidines – Chemistry – the trypanocidal action of diamidines is related to the Amadine or Guanyl structure. Examples are Dininazene aceturate, Phenamidine, Stilbamidine and Pentamidine.

Diminazene aceturate -

- It is odourless
- Yellow powder
- Soluble in water
- Slightly soluble in organic solvents.

Mechanism of action –

- It binds irreversibly but not directly. It binds to the groove between the complementary strands of DNA – regular intervals and thus distorts the helical structure.
- It affects the phospholipids synthesis
- It is said to displace magnesium ion and it inhibits polyamines in the parasite.
- The drug is said to have dyskinetoplastic effect in the parasites.
- The drug interferes with glycolytic pathway of the parasite.

Indication and Uses

- Trypanosomosis in early stage
- Babesicidal effect or in babesia infection.
- It has bactericidal effect against *brucella* and *streptococcus*.

Limitations

- The drug is not effective in late stages of trypanosomosis
- There are report of resistance to the drug and relapse of infection
- It is ineffective against *Trypanosome evansi* in camels at 3.5mg/kg

- Special dose regimen is required for *T.brucei* infection.

Side Effects

- Local reactions in horses and rats might occur at site of injection.
- Neurotoxicity in dogs especially exotic breeds, ataxia, convulsion.
- Nephrotoxicity may be induced by the drug.
- Hepatic impairment

PHARMACOKINETICS

- It is poorly absorbed orally
- But the drug is rapidly absorbed intramuscularly and subcutaneously.
- Distribution of the drug in the tissues is rapid and wide
- Dimidines accumulate in the liver for months, like wise in the kidney and the adrenal glands respectively

Dose

For babesia and trypanosome infection a single intramuscular injection of 3.5mg/kg of 7 percent freshly prepare aqueous solution.

T. brucei infection requires 7mg/kg against *Babesia cabali* and *B. equi*., two doses (5 and 12mg/kg) are given apart

Today, Dimirazene aceturate is formulated with phenazone (8.75%), an antipyretic and analgesic to reduce the pain at the site of the injection.

PENTAMIDINE.

Pentamidine isethionate is preferred drug for prevention and treatment of haemolymphatic stage of human trypanosomosis because the drug does not pass the blood – brain barrier; it therefore is not used to treat CNS involvement.

STILBAMIDINE ISETHIONATE

This drug has anti protozoal and antifungal activity. It is effective in blastomycosis and it is used in the treatment of human visceral leishmaniasis and early stage of sleeping sickness. It is more toxic then pentamidine.

PHENANTHRIDINES

History:

Phenanthridinium derivatives were introduced in 1938

The first active agents are phenidium and dimidium. This drugs exhibited photosensitization and other toxicities. Other agents replaced this drugs that are associated with toxicities, the less toxic homidium amd isometamidium are now in use.

Mode of Action

The phenanthridines bind strongly with D.N.A. especially kinetoplast D.N.A.

- They interfere with glycosomal functions.
- They interfere with function of unusual adenosine monophosphate – binding protein.
- They may cleave K.D.N.A. – topoismerase complexes this result to dyskinetoplastic trypanosome
- Homidium is mutagenic and trypanosomes exposed to it for one hour may retain motility for 24hours, but are no longer infective

PHARMACOKINETICS

- They are poorly absorbed orally

- They are rapidly absorbed when injected intramuscularly
- It is eliminated in 24hours
- Isometamidium administered it could for a tissue depot at the site of injection. The drug therefore is very slowly absorbed giving effective protection for up to 6months
- Distribution is wide and prolonged the drug accumulates in the liver.

Uses:

Horndium is active against

- *T.vivax, T.congolense* and less active against *T. brucei.*
- *T.evansi* and *T.cruzi* has been reported to respond to carlidium another member of the group of Homidium salt.

Dose

Homidium is available as the bromide and the more water – soluble chloride salts. A single dose of 1.0mg/kg of a 2% solution is given 1/m. in to the neck or