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Antifungals

Antifungals :- are chemicals used to treat diseases caused by fungi (mold or yeast)

Fungi, protozoans, and multicellular parasites are more complex than bacteria. Because of structural and functional differences, most antibacterial drugs are ineffective against fungi. Although there are fewer medications to treat these types of infections, the available drugs are usually effective.

Most exposure to pathogenic fungi occurs through inhalation of fungal spores or by handling contaminated soil. Thus, many fungal infections involve respiratory tract, the skin, hair, and nails. In additions, the lungs serve as a route for invasive fungi to enter the body and infect internal organs.

• Some fungal diseases are superficial (Ringworm); others are systemic (Blastomycosis: a fungal infection caused by the organism *Blastomyces dermatitidis*.) .

- **Categories of antifungals include:**

1- Polyene antifungals :

A polyene is a molecule with multiple conjugated double bonds. The polyene antimycotics bind with sterols in the fungal cell membrane, principally ergosterol. This changes the transition temperature of the cell membrane, thereby placing the membrane in a less fluid, more crystalline state.

Ergosterol is a sterol found in cell membranes of fungi and protozoa, serving many of the same functions that cholesterol serves in animal cells. Because many fungi and protozoa cannot survive without ergosterol, the enzymes that create it have become important targets for drug discovery.

As a result, the cell's contents including monovalent ions (K+, Na+, H+, and Cl-), small organic molecules leak and this is regarded one of the primary ways cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible. Examples :

Amphotericin B:

- Used IV for systemic mycoses.
- Amphotericin B is extremely nephrotoxic, is light sensitive, and can precipitate out of solution. However, at therapeutic doses, some amphotericin B may bind to animal membrane cholesterol, increasing the risk of human toxicity.

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Amphotericin B is nephrotoxic when given intravenously. As a polyene's hydrophobic chain is shortened, its sterol binding activity is increased. Therefore, further reduction of the hydrophobic chain may result in it binding to cholesterol, making it toxic to animals.

Antifungal Activity: Amphotericin B is a broad-spectrum antifungal agent. It has activity against yeasts including; Candida albicans and Cryptococcus neoformans; molds, Aspergillus fumigatus.
Clinical Use: Amphotericin B remains the drug of choice for nearly all life-threatening mycotic infections. Used as the initial induction regimen for serious fungal infections (immunosuppressed patients, severe fungal pneumonia, and cryptococcal meningitis with altered mental status).
Adverse Effects: The toxicity of amphotericin B which may occur immediately or delayed include fever, chills, muscle spasms, vomiting, headache, hypotension (related to infusion), renal damage associated with decreased renal perfusion (a reversible) and renal tubular injury (irreversible). Anaphylaxis, liver damage, anemia occurs infrequently.

- **Nystatin**

Nystatin has similar structure with amphotericin B and has the same pore-forming mechanism of action. It is too toxic for systemic use and is only used topically. It is not absorbed from skin, mucous membranes, or the gastrointestinal tract. Nystatin is active against most Candida species and is most commonly used for suppression of local candidal infections. Nystatin is used in the treatment of oropharyngeal thrush, vaginal candidiasis, and intertriginous candida infections.

- **Filipin** – 35 carbons, binds to cholesterol (toxic)
- **Hamycin**
- **Natamycin** – 33 carbons, binds well to ergosterol
- **Rimocidin**

2- Imidazole antifungals :

Azole antifungal activity results from the reduction of ergosterol synthesis by inhibition of fungal cytochrome P450 enzymes. The specificity of azole drugs results from their greater affinity for fungal than for human cytochrome P450 enzymes. Imidazoles exhibit a lesser degree of specificity than the triazoles, accounting for their higher incidence of drug interactions and side effects.

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Azoles are active against many Candida species, Cryptococcus neoformans, the endemic mycoses (blastomycosis, coccidioidomycosis), the dermatophytes, and, Aspergillus infections

Examples:

- **Ketoconazole:** used for superficial infections.
- **Miconazole:** used for superficial infections.
- **Itraconazole:** used for superficial and systemic infections.
- **Fluconazole:** used for systemic and sometimes superficial infections.

3- Antimetabolic antifungals

: Work by interfering with the metabolism of RNA and proteins**.** Example :

- **Flucytosine :** usually used in combination with other antifungals.

4- Allylamines antifungals :

Allylamines inhibit squalene epoxidase, another enzyme required for ergosterol synthesis.

Example :

- **Amorolfin**
- **Butenafine**
- **Naftifine**
- **Terbinafine**

5- Superficial antifungals

: Work by disrupting fungal cell division, Example:

- **Griseofulvin :** an oral medication used to treat dermatophyte infections (Ring worm).

6- Other antifungals:

- **Lufenuron:** is used to treat ringworm in cats.
- **Lyme sulfur:** is used topically to treat ringworm.

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Anti-protozoal Drugs

- They are a class of pharmaceuticals used in treatment of protozoal infections.

Anticoccidial drugs: This group of antiprotozoals is used for treatment or prophylaxis or both against coccidial infections which caused by *Eimeria* Spp.

Groups of Anticoccidial agents:

A- Miscellaneous Anticoccidial agents :

Sulfanomides:

- Sufanomides are active against schizonts.
- They are coccidiostatic at low doses and coccidiocidal at higher doses.
- Examples; **Sulfanomide, Sulfaquinoxaline** and **Sulfadimethoxin**.

Nitrofurans:

- Used for prophylaxis
- They are active against *Eimeria* and *Histomonas.*
- Examples; **Furazolidone** and **Nitrofurazine.**

Amprolium:

- A structural analogue of thiamine (vitamin B_1) competitively inhibits thiamine utilization by the coccidia.
- It acts primarily upon the first generation schizont in the cells of the intestinal wall, preventing differentiation of the metrozoites. It may also suppress the sexual stages and sporulation of the oocysts.

Toltrazuril:

- Toltrazuril (Baycox®) damages all intracellular development stages of *Eimeria*.
- It acts against all species of *Eimeria* and it is coccidiocidal.

B - Ionophore antibiotics:

- The mechanism of action of this group is illustrated by forming complexes with cations such as: Li^+, Na^+, K^+, Mg^{+2} and Ca^{+2}, then this Ionophores carrying these cations to inside of the schizont, thereby effect on the ionic balance of the schizont, consequently rupture of the schizont.
- Ionophores allow birds to develop immunity to *Eimeria* (Immune modulaters).
- Examples; **Monensin**, **Narasin**, **Salinomycin**, **Maduramicin**, **Semduramicin** and **Lasalocid**.

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C- 4 - Hydroxyquinolones:

- This group acts by disruption of mitochondrial cytochrome system of coccidia in the sporozoite stage.
- Examples ; **Clopidol, Decoquinate**, and **Methylbenzoquate.**

Antibabsial drugs : a group of drugs are used to treat *Babesia* Spp. Infections.

Imidocarb and **Amicarbalide:**

- Is effective against *Babesia* spp. infection. It is a cholinesterase inhibitor. It appears to act directly on the protozoa leading to an alteration in morphology.

Diminazene (Berenil®):

- Acts by interfering with glycolysis as well as with DNA synthesis of *Babesia*.

Quinuronium Sulfate (Acaprin®):

- Its mode of action is unclear yet.
- It has a low therapeutic index and may stimulate parasympathetic nervous system , excessive salivation, frequent urination, or dyspnea caused by anticholinesterase activity.

Antitheileriosis: a group of drugs are used to treat *Theileria* Spp. Infections.

Chlortetracycline and **Oxytetracycline:**

- They are used for prophylaxis and may reduce parasitaemia by arresting schizogony.

Hydroxynapthoquinones:

- They are used for the treatment of theileriosis in cattle.
- Napthoquinones are thought to interfere with protozoan mitochondria.
- Examples; **Buparvaquone (Butalex®)** and **Parvaquone (Parvexon®)**.

Antitrypanosomal drugs : a group of drugs are used to treat *Trypanosoma* Spp. Infections.

Diminazene and **Isometamidium:**

- These drugs appear to bind to parasite DNA and block DNA and RNA synthesis.
- They are may be used therapeutically, or for prophylaxis, or both.

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Suramin:

- The mechanism of action is not clear but it thought that it acts by inhibition of many enzymes in the protozoa.
- Suramin is not absorbed orally; therefore it administrated parentrally through I.V. route only because it's irritating nature when given through I.M. or S\C. routes.

Isometamidium chloride (Samorin®) and Homidium:

- They act by interaction with protozoal DNA activities.

Antitoxoplasmosis drugs: a group of drugs are used to treat *Toxoplasma* Spp. Infections.

Sulfanomide and **Trimethoprim.**

Clindamycin and **Clarthromycin.**

Antitrichomonal drugs: a group of drugs are used to treat *Trichomonas* Spp. Infections.

Nitroimidazole derivatives:

- They act by interaction with protozoal DNA activities.
- Examples; **Metronidazole**, **Ronidazole**, and **Carnidazole.**

Antihistomoniasis drugs: a group of drugs are used to treat *Histomonas* Spp. Infections.

Dimetridazole:

- It is one of the Nitroimidazoles and it appears to interfere with RNA synthesis.
- Also it can be used as Antitrichomonal agent too.

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Drugs used in the treatment and control of Parasitic Infections

In this section we shall talk about the most common drugs which used for treatment of parasitic infections which either Endoparasites or Ectoparasites.

I- Drugs used in the treatment and control of Endoparasites

A. Drugs for round worms (Anti-nematodes):

This group is used for treatment of ***Nematodes*** and the main used drug groups for this purpose are:

Avermectins and Milbemycins

- Natural or semi-synthetic agents derived from *Streptomyces avermitilis* and *Streptomyces cyanogriseus*.
- Mechanism of action includes interfering with parasite nerve transmission.
- They are effective against a wide range of nematode species and developmental stages, but have no activity against trematodes or cestodes.
- In addition to killing an existing parasite population, the Avermectins and Milbemycins prevent re-infection for a period after treatment.
- ***Avermectins*** include **Abamectin**, **Doramectin**, **Eprinomectin**, **Ivermectin**, and **Selemectin**. ***Milbemycins*** include **Milbemycin oxime** and **Moxidectin**.

Benzimidazoles:

- They interrupt parasite energy metabolism.
- Most Benzimidazoles are effective against larval and adult roundworms.
- All Benzimidazoles are contraindicated in case of pregnancy because of their ability to penetrate the blood-placental barrier; consequently they cause teratogenic problems.
- Examples; **Albendazole, Fenbendazole, Flubendazole, Mebendazole, Oxfendazole, Oxibendazole** and **Tiabendazole.**

Imidazothiazoles:

- They act by interfering with parasite nerve transmission causing muscular spasm and rapid expulsion.

- **Levamisole** is the active isomer of **Tetramisole** and is therefore more potent and has a wider safety margin.

Organophosphorus compounds (OPC):

- They act by inhibiting cholinesterase thereby interfering with neuromuscular transmission in the parasite.
- They are effective against adult gastro-intestinal roundworms but ineffective against migrating larvae, tapeworms, or flukes.
- Clinical signs of toxicity such as salivation and diarrhea may occasionally occur, particularly in foals.
- Examples; **Haloxon, Dichlorvos**, **Naftalofos**, and **Metrifonate .**

Tetrahydropyrimidines:

- They interfere with parasitic nerve transmission as cholinergic stimulants, leading to neuromuscular spastic paralysis. This mode of action is similar to that of the Imidazothiazoles.
- Examples; **Morantel**, **Oxantel,** and **Pyrantel .**

Piperazine:

- It modifies neurotransmission in parasites causing expulsion of the parasite.
- Piperazine is used for treatment of some gastro-intestinal roundworms such as *Toxocara* and *Uncinaria* in dogs and cats.

Diethylcarbamazine:

- The mechanism of action of this drug is similar to Piprazine.
- Is active against adult ascarids but is more frequently used as a heartworm prophylactic.

B. *Drugs for tapeworms (Anti-cestodes):*

This group is used for treatment of ***Cestodes*** and the main used drug groups for this purpose are:

Praziquantel:

- It acts by increasing ion influx across the parasite tegument leading to immediate muscle spasm.
- Praziquantel is effective against all tapeworms in dogs and cats and is preferred in most *Echinococcus* control programmers.

- Also it is active against *Moniezia* in sheep and against *Anoplocephala* and *Anoplocephaloides* in horses.

Niclosamide:

- It acts by interfering with adenosine triphosphate (ATP) production.
- It has a little efficacy against *Echinococcus* and variable activity against *Dipylidium*.

Benzimidazoles:

- **Albendazole, Fenbendazole, Mebendazole,** and **Oxfendazole** are effective for tapeworm control in ruminants. **Fenbendazole** and **Mebendazole** also control some tapeworms in dogs and cats.

C. Drugs for flukes (Anti-trematodes):

This group is used for treatment of ***Trematodes*** and the main used drug groups for this purpose are:

Benzimidazoles:

- **Albendazole** and **Netobimin** are active against *Fasciola,* they are effective against adult stages.
- **Netobimin** is also effective against adult *Dicrocoelium dendriticum.*
- **Triclabendazole** is highly effective against all liver stages of *Fasciola*.

Clorsulon:

- It is a Sulfonamide and competitive inhibitor of important enzymes for energy metabolism in flukes.
- It is used in cattle for control of liver fluks.

Oxyclozanide and Rafoxanide:

- They act by interfering with adenosine triphosphate (ATP) production.
- **Oxyclozanide** is mainly active against adult flukes. While **Rafoxanide** is active against adult and immature flukes aged 6 - 8 weeks and older.

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II- Drugs used in the treatment and control of Ectoparasites

The most common ectoprasiticides that used in veterinary practice are:-

Amidines\ *Topical*

- They act by increasing of the nervous activity in the ectoparasite.
- They active against lice, mites, and ticks on cattle; lice, and ticks on sheep; lice and mites on pigs; *Demodex* and *Sarcoptes* on dogs.
- Side effects include CNS depression.
- Example; **Amitraz.**

Avermectins and Milbemycins\ *Parentral*

- Discussed previously, see the section of Anti-nematodal drugs.
- They are active against a wide range of immature and mature nematodes and arthropods among all animal species approximately.

Carbamates\ *Topical*.

- They are revisable acetylcholine esterase (Ach*E*) inhibitors in the ectoparasite.
- They are indicated for Fleas on dogs, cats and birds.
- The main side effect is the carcinogenicity.
- Examples; **Bendiocarb**, **Carbaril**, and **Propoxur.**

Neonicotinoids:

-They bind to the nicotinic receptors in the ectoparasite leading to paralysis and death of that ectoparasite.

- They are indicated for Fleas on dogs, cats, and rabbits.
- Side effects include transient salivation in the topical forms of Neonicotinods and pruritis in the entral forms of them.
- Examples; **Imidacloprid** (topical) and **Nitenpyram** (entral).

Organophosphorus compounds (OPC)\ *Topical*:

- They are irreversible acetylcholine esterase (AchE) inhibitors in the ectoparasite.
- Most members of this group are indicated for scab, flies larvae, lice, and ticks.
- The main side effect of this group is its irreversible acetylcholine esterase (Ach*E*) inhibitory effect on the host. **Examples; Azamethiphos, Chlorpyrifos, Clofenvinfos, Coumafos, Dichlorvos, Dimpylate (Diazinon), Ethion, Fenitrothion,Heptenophos, Malathion, Metrifonate, Phoxim, Propetamphos, Temefos, and Tetrachlorvinphos.**

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Phenylpyrazoles\ *Topical*

- They act by blocking of GABA resulting in rapid death of the ectoparasite.
- They indicated for fleas, lice, mange and ticks.
- Side effects include transient hypersalivation.
- Example; **Fipronil.**

Pyrethrins and synthetic pyrethroids\ *Topical*

- They exert their action on the sodium channels of parasite nerve axons, causing initial excitement then paralysis.
- Most members of this group are indicated for Flies on horses and cattle; lice on horses, cattle and goats; flies strike, biting lice, ticks, headflies, and *Psoroptes* (dip) on sheep; red mites on poultry.
- Side effects include: Minor signs of discomfort with some cattle up to 48 hours after treatment; rarely skin lesions and hair loss in dogs; rarely uncoordinated movements, tremor, hypersalivation, vomiting, rigidity of hindquaters in dogs if chew collar.
- Examples; Natural **Pyrethrins** extracted from *pyrethrum* flowers and the synthetic pyrethroids **Bioallethrin**, **Cyhalothrin, Cypermethrin**, **Deltamethrin**, **Fenvalerate**, **Flumethrin**, **Lambdacyhalothrin**, **Phenothrin,** and **Permethrin .**