

Antiparasitic Agents:-

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INTRODUCTION of Anthelmintic :-

Antiparasitics are drugs which kill or inhibit the growth of parasitic organisms.

A. Mechanisms of action

1. Paralysis of parasites by mimicking the action of putative neurotransmitters .

2. Alteration of metabolic processes.

- a. Inhibition of microtubule synthesis.
- b. Inhibition of folic acid synthesis or metabolism.
- c. Inhibition of thiamine utilization.
- d. Uncoupling of oxidative phosphorylation.
- e. Inhibition of chitin formation in arthropods.
- f. Simulation of insect juvenile hormones.

3. Alteration of parasite reproduction.

- a. Inhibition of replication in protozoans.
- b. Inhibition of egg production in nematodes.

B. Characteristics of ideal antiparasitics:-

- 1. Effective in removing parasites from body.
- 2. Wide therapeutic index: Toxic dose $> 3\times$ therapeutic dose.
- 3. Economically justifiable.
- 4. Easy to administer, for example, in feed, injections, and pour-on
- 5. One-dose treatment.
- 6. No residue problems, especially in food-producing animals.
- 7. Effective against immature form of parasites.

C. Disadvantages of antiparasitics

- 1. Expense.
- 2. Development of resistant strains.
- 3. Inhibition of host immunity.

D. Current trends include the use of broad-spectrum drugs and combination therapy to increase efficacy.

ANTINEMATODAL DRUGS (NEMATOCIDES):-

May be broad-spectrum or narrow spectrum.

A. Classification of antinematodal drugs

- 1- Benzimidazoles.
- 2- Ivermectin.

- 3-Milbemycins.
- 4-Imidazothiazine.
- 5-Levamisole
- 6-Organophosphorus compound.
- 7-Tetrahydropyrimidines.
- 8-Piprazine.
- 9-Diethylcarbamazine.
- 10-Phenothiazine.

1-Benzimidazoles (BZDs)

Thiabendazole is the prototypical agent. It is approved for use in ruminants and horses.

Preparations. **Thiabendazole** is the prototype of BZD, which is much less potent than other BZDs, and is no longer used as a nematocide.

Other BZDs include:-

albendazole, fenbendazole, oxfendazole, oxibendazole, and febantel (a pro-BZD that is converted to fenbendazole and oxfendazole in animals).

Mechanism of action. BZDs inhibit microtubule synthesis in nematodes cell by interfering with polymerization of β -tubulins. BZDs do not affect microtubule synthesis in animal cells, this is why these drugs are relatively safe in animals.

Care should be exercised for some of the BZDs (albendazole) if the animal is in the first one-third of pregnancy.

Therapeutic uses

(1) **Ruminants.** Albendazole, fenbendazole, and Oxfendazole are effective against major GI worms (in both the adult and larval stages). and In addition, they are effective against lungworms, against filariae.

(2) **Horses.** Fenbendazole, oxfendazole, and oxibendazole are effective against strongyles.

(3) **Swine.** Fenbendazole is effective against *Ascaris*.

(4) **Dogs and cats.** Fenbendazole and febantel are effective against ascarids, hookworms, and whipworms in both adult and larva forms.

(5) BZDs have ovicidal activity on nematodes. In addition, production of eggs by nematodes is inhibited within 1 hour of BZD administration.

Adverse effects:- These agents are generally safe, although albendazole

may be teratogenic and embryotoxic. BZDs may be toxic to liver and bone marrow in dogs, particularly at high doses.

2. Ivermectin.

It is extracted from **Streptomyces avermitilis**. The ivermectin injectable is dissolved in propylene glycol–glycerol formal mixture.

Therapeutic uses and administration

(1) **Ruminants.** Ivermectin is effective against all major GI worms and lungworms.

(2) **Horses.** It is effective against both, stomach worms, strongyles, pinworms, and ascarids.

(3) **Pigs.** Ivermectin is effective against major GI worms, lungworms.

(4) **Dogs** Ivermectin is effective against ascarids, hookworms, and whipworms.

Ivermectin is potent substrates and inhibitors of the P-glycoprotein in dogs.

Ivermectin are used as a heartworm prevention and are administered to dogs once a month.

All species. Ivermectin is effective against all ectoparasites. It is used especially to control mites.

3-Milbemycins.

is extracted from *Streptomyces hygroscopicus aurocriminosus*.

Therapeutic uses. Milbemycin is approved for use in dogs only and is effective against the hookworms, whipworms, and ascarids.

Milbemycin may be used in all dog breeds, including Collies, and is safe in pregnant dogs and breeders (because it is a weak substrate of P-glycoprotein).

Adverse effects. Milbemycin has a high safety margin in dogs.

However, milbemycin-killed microfilaria can cause hypersensitivity manifested by lethargy, pyrexia, salivation, emesis, coughing, tachypnea, and/or shock.

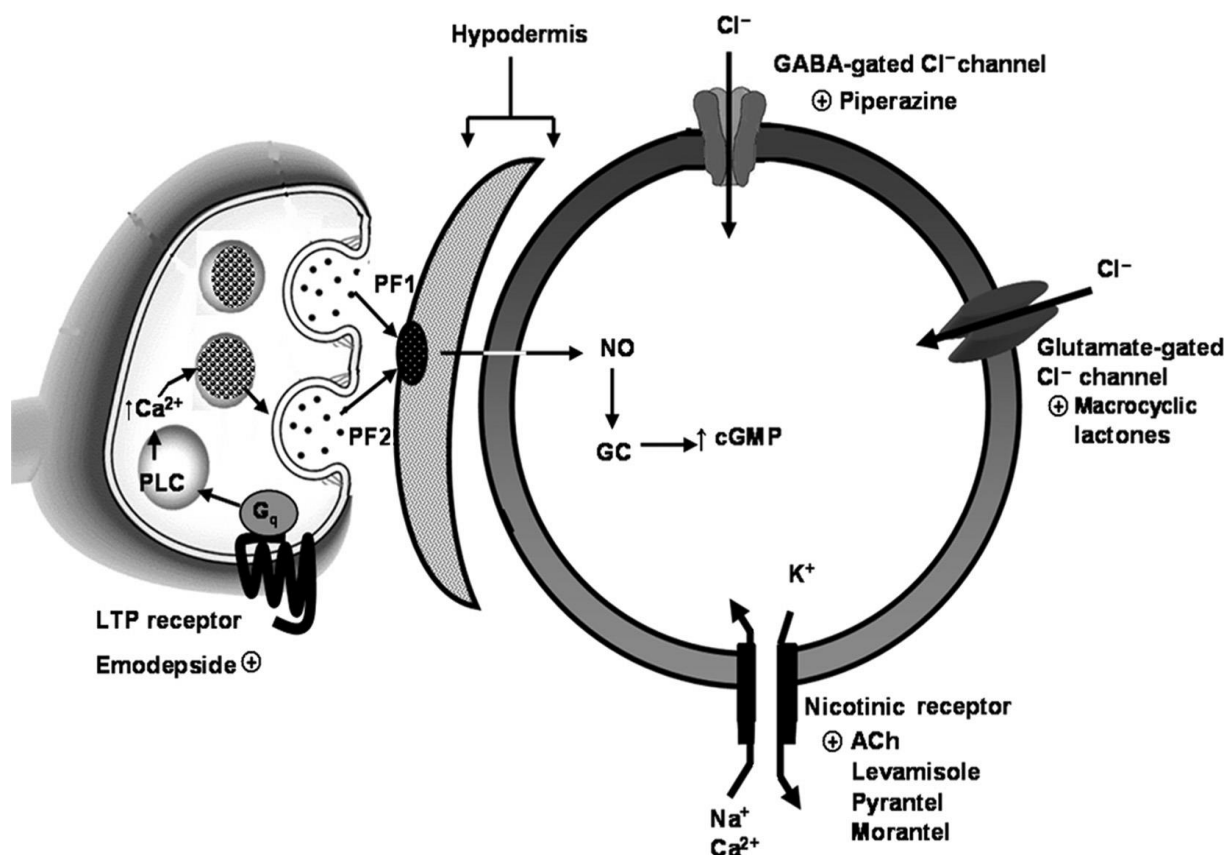
4-Imidazothiazine.

5-Nicotinic agonists: Levamisole.

Levamisole:- is approved for use in ruminants and pigs.

Mechanism of action. Levamisole paralyzes worms by selectively activating nematode nicotinic acetylcholine (ACh) receptors, allowing

entry of Na^+ , Ca^{2+} , for excessive body muscle contraction, and thus induces paralysis.



Mechanisms of action of antinematodal drugs that interfere with parasite Nervous system.

LTP = latrophilin; PLC = phospholipase; PFI = SDPNFLRF-amide; PFZ = SADPNFLRF-amide; GC = guanylyl cyclase.

Therapeutic uses

(1) **Ruminants.** Levamisole is effective against most mature GI worms and lungworms, but it has marginal activity against *Strongyloides* and immature GI worms.

(2) **Pigs.** It is effective against ascarids, *Strongyloides*, nodular worms, lungworms, and kidney worms.

Adverse effects. Levamisole is one of the most toxic anthelmintics. It has a low safety margin, especially when given by injection. Do not administer to dairy cattle of breeding age, since milk withdrawal periods in these animals have not been determined.

Signs of levamisole poisoning:-

1-include parasympathetic stimulation, convulsions,CNS depression ,and asphyxia, which is primarily the result of respiratory muscle paralysis .

2-Atropine cannot counteract levamisole-induced depolarizing blockade of skeletal muscle; therefore, it is not an antidote for levamisole overdose.

3- Coadministration of levamisole and pyrantel, another nicotine-like nematocide,increases toxicity.

6- Piperazine

Mechanism of action:-

Piperazine is a GABA-receptor agonist that hyperpolarizes nematode muscle, causing flaccid paralysis of worms .

Therapeutic uses.

Piperazine has a limited spectrum of action but is effective against ascarids and nodular worms in all species; however, its use is limited in ruminants, because ascarids are not a significant problem in this species.

Adverse effects

Piperazine is a safe drug, but large doses may produce vomiting, diarrhea, and ataxia. The ataxia is due to a GABA-mimetic effect of piperazine on CNS neurons and is particularly seen in young animals given high doses.