

University of Karbala

College of veterinary medicine

Second semester
Pharmacology Lect. # 5

**Chemotherapy of parasitic diseases (Antinematodal,
anticestodal, and antiprotozoal drugs)**

Part one

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General principles: Antiparasitics are drugs that reduce burdens to a tolerable level by killing parasites or inhibiting their growth. The ideal antiparasitic has the following characters:

- a. Effective in removing parasites from body
- b. A wide therapeutic index (i.e., the toxic dose is at least three times the therapeutic dose);
- c. Is effective after one dose;
- d. Is easy to administer (e.g., in feed, injection, and pour-on);
- e. Effective against immature form of parasites;
- f. Is inexpensive; and
- g. Does not leave residues (an important consideration for use in food-producing animals).

Mechanisms of action:

1. Paralysis of parasites by mimicking the action of putative (assumed) neurotransmitters (Table 1).
 2. Alteration of metabolic process
 - 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
- I. Antinematodal drugs (Nematocides):** May be broad-spectrum or narrow spectrum.

Classification of antinematodal drugs:

A. Benzimidazoles

B. Nicotinic agonists: levamisole, pyrantel, morantel

- C. **Macrocyclic lactones:** ivermectin, doramectin, eprinomectin, selamectin, milbemycin, moxidectin
- D. **Miscellaneous nematocides:** dichlorovos, piperazine, emodepside, melarsomine

Table1. Putative classical neurotransmitters of various parasites

Parasite	Excitatory	Inhibitory
Nematode	ACh, Glu	Glu, GABA
Cestode	5-HT	ACh
Trematode	5-HT	ACh, DA, NE
Arthropod	ACh, Glu	Glu, OA, GABA

ACh, acetylcholine; DA, dopamine; GABA, γ -aminobutyric acid; Glu, glutamate; NE, norepinephrine; OA, octopamine; 5-HT, serotonin

A. Benzimidazoles (BZDs (Figure 1)

- a. **Thiabendazole:** is the prototypical agent, which is approved for use in ruminants and horses. It is much less potent than other BZDs and is no longer used as a nematocide. Other BZDs include **albendazole, fenbendazole, oxfendazole, oxibendazole, and febantel.** All of BZDs, except thiabendazole, have a side chain at position 5, which prevents hydroxylation of position 5 of the BDZs. Therefore, these compounds are more potent than thiabendazole as nematocides

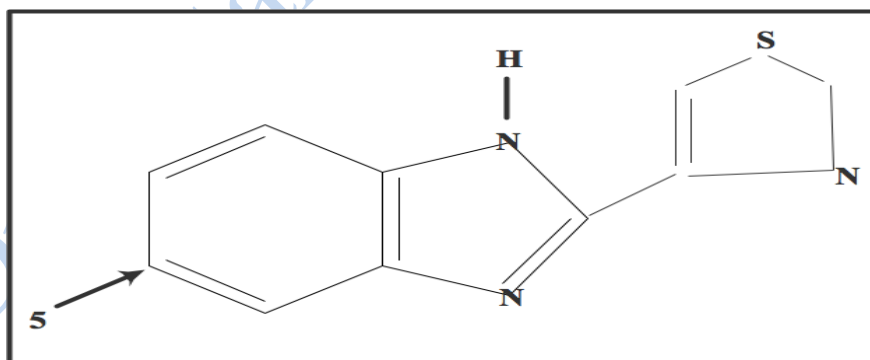


Figure1. Chemical structure of thiabendazole. Metabolism occurs via hydroxylation at position 5. The other benzimidazoles are more potent than thiabendazole because they have a side chain, which prevents hydroxylation at position 5.

Mechanism of action: They inhibit microtubule synthesis in nematode cells by interfering with polymerization of β -tubulins (Figure 2). BZDs do not affect microtubule synthesis in animal cells, which explains why these compounds are safe for use in animals.

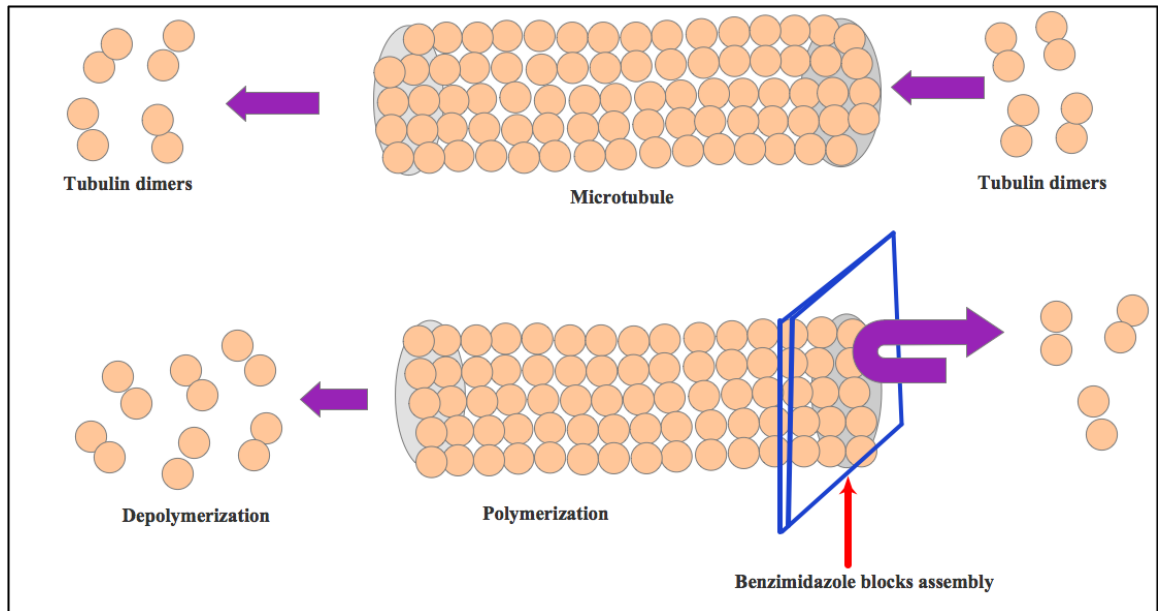


Figure 2. BZD-induced inhibition of microtubule synthesis in helminthes.

BZDs bind β -tubulin of helminthes, preventing dimerization with α -tubulin and polymerization of tubulin oligomers into microtubules.

Therapeutic uses:

Ruminants: Albendazole (Valbazen®), fenbendazole (Panacur®), and oxfendazole (Benzelmin®, Synanthic®) are effective against major GI worms in both adult and larval stages. In addition, they are effective against lungworms. However, they are ineffective against filariae.

Horses: Fenbendazole (Valvazen®) and oxibendazole (Anthelcide®) are effective against *Stongylus* with limited activity against immature *Stongylus*. They are not very effective against migrating larvae of *Stongylus vulgaris* and *S. edentatis*. They are effective against *Oxyuris*, *Trichostrongylus*, and *Parascaris*. They are not effective against *Gasterophilus*.

Dogs and cats: Fenbendazole and febantel (in Drontal Plus®) are effective against ascarids, hookworms, and whipworms in both adult and larva forms.

Administration: BZDs are administered orally. In general, one single dose in cattle and horses, and three to five consecutive daily dosages in carnivores and omnivores.

Pharmacokinetics:

Absorption: absorption of BZDs for GI varies, depending on the water solubility of the compound; the ones with better water solubility, such as albendazole and oxbendazole have better GI absorption than others. Since bile can help dissolve BZDs, absorption of them will be best in animals with a full stomach.

Metabolism: In general, all BZDs, except thiabendazole, are resistant to metabolism. Albendazole can be converted to its sulfone or sulfoxide metabolites; these metabolites are also active.

Excretion: The majority of BZDs with the exception of thiabendazole and albendazole are excreted unchanged in feces.

Drug resistance: Cross-resistance occurs among all BZDs.

Adverse effects: BZDs compounds are generally safe for use, although albendazole may be teratogenic and embryotoxic.

B. Nicotinic agonists:

A. Levamisole:

Mechanism of action: It paralyzes the parasite by selectively activating nicotinic ACh receptor of the nematode, allowing entry of Na^+ , Ca^{2+} which causing massive muscle contraction, and consequently paralyses.

Therapeutic uses: In ruminants, levamisole is effective against most mature GI worms and lungworms, but it has marginal activity against *Strongyloides* and immature GI worms.

Pharmacokinetics: Levamisole has excellent absorption after oral, parenteral, or topical administration. In cattle, levamisole is metabolized by liver into metabolites formed by oxidation of imidazole ring and opening of thiazolidine ring. More than 90% of levamisole is excreted as metabolites

into urine and 10% in feces. The preslaughter clearance periods in cattle are 48-72 hours (PO) and 7 days (SC), and 11 days (topical).

Adverse effects: levamisole is one of the most toxic anthelmintic. It has a low safety margin, especially when given by injection. It should not be given to dairy cattle of breeding age, since milk withdrawal periods in these animals have not been determined. Signs of toxicity include parasympathetic stimulation, convulsions, CNS depression, and asphyxia.

B. *Pyrantel and morantel:*

Pyrantel is inactivated in aqueous solution upon exposure to light, thus it should be stored in light-resistant containers. The drug should be used soon after the preparation of a drench solution or suspension. Morantel is the methyl ester of pyrantel and is stable in solution.

Mechanism of action: Pyrantel and morantel paralyze worms by causing depolarizing neuromuscular blockade. The mechanism is similar to that of levamisole (Figure 3)

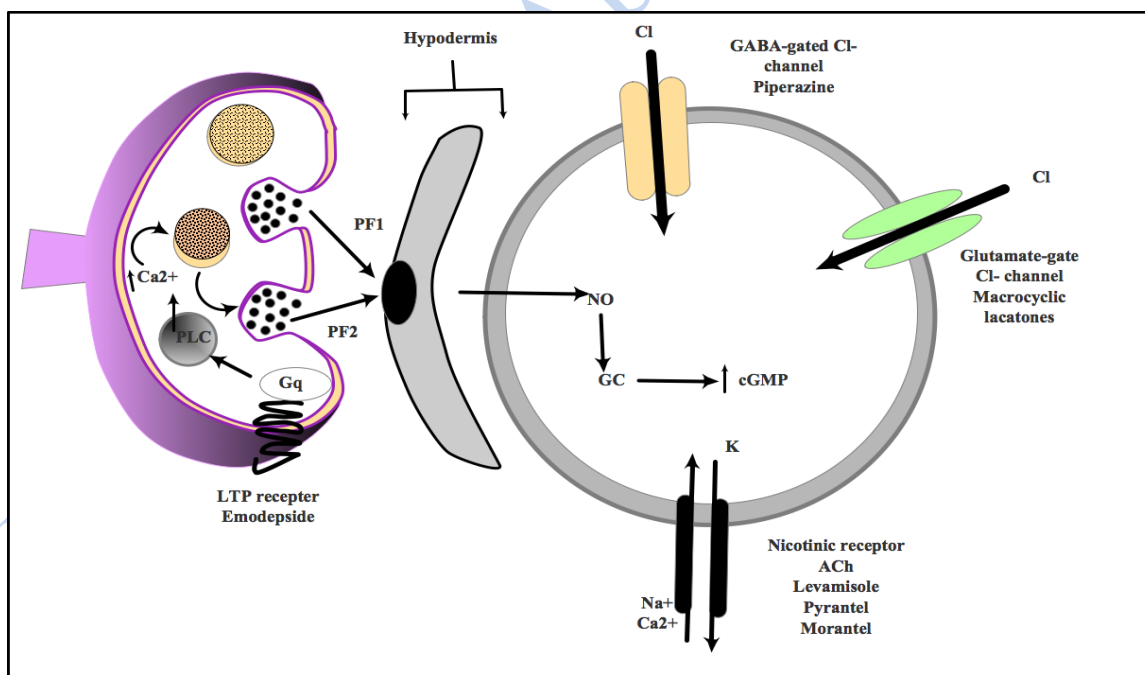


Figure 3. Mechanisms of action of antinematodal drugs that interfere with parasite nervous system. LTP (latrophilin); PLC (phospholipase C); PFI (SDPNFLRF-amide); PFZ (SADNFLRF-amide); GC (guanylyl cyclase)

Therapeutic uses:

- a. **Horses:** Pyrantel is effective against strongylus, ascarids, and pinworms. Tartrate preparation of pyrantel is used to prevent nematodes infestation and pyrantel pamoate is used to treat nematodes infestation.
- b. **Dogs and cats:** Pyrantel is effective against all GI nematodes, but it has limited efficacy against whipworms.
- c. **Ruminants:** Morantel is used as a feed additive, which is effective against stomach worms, nodular worms, and other principal intestinal worms.

Pharmacokinetics: Since pyrantel tartrate is water soluble, it is well absorbed from GI tract following oral administration. Morantel tartrate is absorbed rapidly from the abomasum and small intestine.

Metabolism and excretion: The absorbed pyrantel and morantel are rapidly metabolized by hydroxylation and conjugation and excreted mostly by feces and urine. Preslaughter withdrawal requirements are 14 days for pyrantel tartrate in cattle

Adverse effects: Are not common at the recommended doses. However, when they occur, they are similar to those of levamisole toxicity.

Contraindications: since morantel and pyrantel have the same mechanism of action as levamisole, these agents should not be administered concurrently.

C. *Macrocyclic lactones (macrolide endectocides):*

Mechanism of action: They activate the glutamate-gated chloride channels, thus inhibiting neurotransmission in nematodes and arthropods to induce flaccid paralysis (Figure 4).

Adverse effect: Macrocyclic lactones have a high safety margin in ruminants and horses and they are also safe in pregnant animals and breeders. CNS depression may occur with high doses. Although macrocyclic lactones activate γ -aminobutyric acid (GABA)-gated Cl^- channels in animals, the GABA-receptor antagonist picrotoxin does not work well as an antidote.

Resistance: Resistances to macrocyclic lactones have occurred in nematodes arthropods. Cross-resistance among macrocyclic lactones can occur.

Examples of Macrocyclic lactones are:

- a. *Ivermectin*
- b. *Dormectin*
- c. *Selamectin*
- d. *Milbemycin*
- e. *Moxidectin*

D. Miscellaneous antinematodal drugs:

- a. ***Dichlorovos (Atgard®)***: It is organophosphate that inhibits ACh breakdown by irreversibly inhibiting ACh esterase.

Therapeutic uses: It is effective against major GI worms such as whipworms, nodular worms, *Strongyloides*, hookworms, and ascarid.

Pharmacokinetics: Dichlorovos it is a lipophilic liquid that is incorporated into polyvinyl chloride resin pellets. As these pellets traverse the GI tract, dichlorovos diffuses into the intestinal fluid, allowing the drug to come into contact with nematodes. The free pellet will pass with feces out of the GI tract.

Adverse effects: Accumulation of ACh by dichlorovos can stimulate cholinergic receptors to induce the SLUDD (salivation, lacrimation, urination, diarrhea, and dyspnea) syndrome. Acute death may result from respiratory paralysis cardiovascular arrest.

- b. ***Piperazine:***

Mechanism of action: It is a GABA-receptor agonist that hyperpolarizes nematode muscle, causing flaccid paralysis of worms (Figure 4).

Therapeutic uses: It is effective against ascarids and nodular worms in all species

Pharmacokinetics: Piperazine salts are well absorbed from the GI tract. The liver metabolizes part of the piperazine and the remainder is excreted in the urine unchanged.

Adverse effects: Piperazine is safe drug, but at 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.

c. **Emodepside:** It is a semisynthetic agent.

Mechanism of action: It is a selective agonist of the presynaptic latrophilin receptor, a Gq-coupled receptor, of nematodes, which increases the release of inhibitory neuropeptides PF1 and PF2, and opens Ca^{2+} -activated K^{+} channels, thereby causing flaccid paralysis of the locomotive and pharyngeal muscles in nematodes (Figure 4).

II. Drugs for heartworm prevention and therapy

Introduction: Treatment and prevention of heartworm involve three aspects as follows:

1. Removal of adult heartworms requires an adulticide
 2. Interruption of the life cycle requires a microfilaricide
 3. Prevention of infection requires a larvicide.
- a. **Melarsomine (Immiticide):** It is a trivalent arsenic compound.

Mechanism of action: It denatures proteins/enzymes by binding to the sulfhydryl groups of cysteine residues.

Pharmacokinetics: Melarsomine is absorbed completely after IM injection and reach peak concentration in blood after 8 minutes. The drug is distributed widely in body tissues but is concentrated in the liver and kidneys.

Melarsomine is metabolized in the liver and excreted into bile. The parent drug and its metabolites are eliminated in feces and urine.

Adverse effects:

- Mild localized edema may occur following IM injection
- Distress, restless, pawing, salivation, vomiting, tachycardia, abdominal pain, hind limb, and weakness may occur.
- Liver toxicity
- Nephrotoxicity

Toxicity can be alleviated by IM administration of dimercaprol (BAL) within 3 hours after onset of toxicity

b. **Microfilaricides:**

c. **Larvicides for heartworm prevention**