

University of Karbala

College of veterinary medicine

Second semester

Pharmacology Lect. # 5

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

Part two

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III. Anticetodal drugs:

These agents kill tapeworms and are called taeniocides. The host animal may digest worms killed by these agents; therefore, the killed worms may not be evident in the feces. Control of intermediate hosts can be considered as away of eliminating the future infection.

a. *Dichlorophene:*

Therapeutic uses: It to treat *Taenia* and *Dipylidium* infestation in dogs and cats.

Administration: It is given orally after an overnight fast.

Mechanism of action: Dichlorophene causes uncoupling of oxidative phosphorylation to deplete ATP from tapeworms.

Adverse effects: Vomiting and diarrhea may be seen after dichlorophene administration.

b. ***Benzimidazoles:*** *Fenbendazole*, *oxfendazole*, and *albendazole* are effective against mature *Taenia* and *Echinococcus* in dogs and cats, and *Moniezia* in ruminants. They may kill intermediate hydatid cysts of *Taenia* in infected cattle and sheep.

c. ***Praziquantel (Droncit®, Drontal®, Drontal® Plus, Zimecterin®, Equimax®, Quest® Plus.***

Therapeutic uses: Praziquantel is effective against all species of tapeworms and kills both adult and juvenile stages of the worms.

Mechanism of action: Praziquantel causes paralysis and digestion of tapeworms as well as irreversible focal vacuolization and disintegration of integument. The mechanism of action involves the selective binding of praziquantel to the β -subunit of the voltage-dependent Ca^{2+} channel of the susceptible parasites. The

increased opening of the channels in the parasite mediates an excessive increase in intracellular Ca^{2+} concentrations and cell autolysis.

Administration: Praziquantel is administered orally or SC in dog, cats, and horses. Fasting before oral administration is necessary.

Pharmacokinetics: Praziquantel is completely absorbed within 2 hours of oral administration. It is distributed throughout the body, including the CNS. Praziquantel is metabolized in liver to unknown metabolites by cytochrome P450 and is excreted in the urine

Adverse effects: Praziquantel has a long history of safe use in animals. However, overdose may induce anorexia, vomiting, salivation, diarrhea, and lethargy in small percentage of animals. It has no teratogenicity or embryotoxicity.

d. Epsiprantel (Cestex®):

Its mechanism of action is similar to that of praziquantel. Unlike praziquantel, epsiprantel is absorbed poorly after oral administration and most of the drug is eliminated in the feces.

e. Pyrantel pamoate:

It is effective against equine tapeworms *Anoplocephala perfoliata* and is administered at 13.2 mg/kg orally. It is not as effective as praziquantel as anticestodal drug.

IV. Antitrematodal drugs

Introduction: Infestation with liver flukes (*Fasciola hepatica*) is the most common and most economically important trematode disease of domestic animals worldwide. Liver fluke disease is typically chronic and subclinical in nature. Both mature and immature liver flukes cause damage to liver. After grazing

ruminants ingest metacercaria, the immature flukes emerge from the cysts, penetrate the small intestine wall, traverse the peritoneal cavity and penetrate into liver within 4 days of infestation. These immature flukes will tunnel through liver tissues growing rapidly. The extensive damage can cause acute clinical signs of fasciolosis, which occur within 6-8 weeks of inoculation. This stage can be fatal. Scar tissues are present after liver is damaged. During the eighth week of infestation, flukes begin to penetrate the bile duct, where they become mature by 10-12 weeks after infestation. These mature flukes cause biliary inflammation and progressive occlusion.

Antitreumatodal drugs are highly lipophilic and most of them are only effective against mature flukes, but not immature flukes, that reside in the liver.

a. Clorsulon (Curatrem®, Ivomec® Plus): It is a sulfonamide that is effective against both mature and immature *F. hepatica* in cattle.

Therapeutic uses: Clorsulon is the most effective drug against *F. hepatica*, killing mature and immature flukes in cattle. However, its activity against *F. magna* is poor and is not effective against rumen or lung flukes.

Mechanism of action: Clorsulon inhibits 3-phosphoglycerate kinase and phosphoglyceromutase in the glycolytic pathway, depriving the fluke of a metabolic energy source.

Pharmacokinetics: After oral administration, clorsulon is absorbed rapidly and reach peak blood concentration within 4 hours after oral ingestion. Little of dosed clorsulon is metabolized, thus the majority of the dose is eliminated in the unchanged form in both feces and urine. The preslaughter withdrawal period is 8 days. Clorsulon should not be used in lactating dairy cattle.

Adverse effects: If used according to the instruction of use, side effects are less likely to occur. It is safe for use in pregnant and breeding animals.

b. Albendazole: Mechanism of action is similar to that of benzimidazole (section I A a). It is effective against mature liver flukes (e.g., *F. hepatica*) in cattle. It requires a 27-days preslaughter withdrawal period. Because it has

teratogenicity effects, albendazole should not be used in pregnant cattle during the first 45 days of gestation or in female dairy cattle of breeding age.

V. Antiprotozoal drugs

The main purpose of this section is to discuss the anticoccidial drugs, drugs for treatment of equine protozoal myeloencephalitis (EPM), toxoplasmosis, giardiasis, babesiosis, and cryptosporidiosis.

A. Anticoccidial drugs:

Coccidiosis, a predominant disease in calves, piglets and poultry, costs the USA poultry industry >50 million dollars annually despite the expenditures of >85 million dollars for anticoccidial drugs. These losses are caused primarily by impaired feed conversion, slow growth, and the poor quality of carcasses at processing.

1. *Decoquinat*: it is a quinolone and is lipophilic

Therapeutic uses:

- It is useful in cattle, sheep, goats, and broilers for the prevention of coccidiosis. It is usually used as feed additive and it is not effective to treat clinical coccidiosis.
- It is effective against all species of coccidian on the sporozoites stage.

Mechanism of action:

It stops the development of the sporozoites or trophozoites of coccidia by inhibiting the electron transport system within parasite mitochondria. This action is coccidiostatic. In addition, it may block DNA synthesis by inhibiting DNA gyrase.

Recommendations:

- Do not feed to sheep, and goats producing milk for food
- Do not use in laying chickens

Adverse effects: No adverse effect produced if the drug is used as recommended

2. *Clopidol (Coyden®)*: It is a pyridinol derivative and is lipophilic drug.

Therapeutic uses:

- It is used as a feed additive to prevent coccidiosis in broilers and replacement chickens
- It is effective against all species of coccidian on the sporozoites stage.
- No preslaughter withdrawal period is required
- No adverse effects are expected if the drug is used under conditions of *recommended use*.

3. Na^+ ionophores:

Drugs in this group include monensin, lasalocid, narasin, salinomycin, and semduramicin. These antibiotics are used exclusively as anticoccidial drugs.

Therapeutic uses: Na^+ ionophores are effective against all coccidia species in chickens, cattle, and goats.

- Na^+ ionophore attack the first generation of trophozoites and schizonts
- The preslaughter withdrawal is not required
- They are not for use in calves
- Monensin and lasalocid are also used as growth promoters

Mechanism of action:

Sodium ionophores facilitate the transport of sodium and hydrogen ions into cells in the rumen, elevating intracellular sodium and hydrogen ions concentrations. As a result, certain mitochondrial functions and ATP hydrolysis are inhibited.

Adverse effects: These drugs may cause severe cardiovascular and skeletal muscular side effects. These adverse effects are due to disturbances in the intracellular sodium, hydrogen and calcium concentrations.

Contraindications: Horses and turkeys are very sensitive to sodium ionophores and they can be fatal if given in high doses accidentally.

4. Diclazuril (Clinacox®)

Mechanism of action: It is effective against schizonts and gametes by inhibiting nuclear division.

Therapeutic uses: Diclazuril is used a feed additive to prevent coccidiosis in broilers. Since it is effective against later stages of coccidia, it has potential in be used treating outbreaks of coccidiosis.

Adverse effects: Diclazuril is a safe drug when used as directed

B. Drugs for the treatment of equine protozoal myeloencephalitis (EPM)

General concepts: Opossum is the definitive host and small mammals including cats, skunks, and raccoons are intermediate hosts. Horse is considered an abnormal, dead-end host for *S. neurona*. Horses are infected by ingestion of sporocysts in contaminated feed or water. The schizonts of the asexual cycle are found in CNS, which cause cerebral damages. The signs of the infection are manifested by head tilt, ataxia, muscle weakness and atrophy, urinary incontinence, and constipation.

1. **Ponazuril (Marquis®):** It is an active metabolite of toltrazuril (sulfone). It is a very potent anticoccidial drug.

Therapeutic uses:

Ponazuril is for the treatment of EPM, coccidiosis, and toxoplasmosis. For the treatment of EPM, administer the drug orally, 5 mg/kg/day, for ≥ 4 weeks.

Mechanism of action: Ponazuril kills schizonts by inhibiting nuclear division.

Pharmacokinetics: After daily administration to horse, ponazuril reaches its peak plasma levels in ~18 days and peak CSF levels in ~15 days. Since it is a lipophilic drug, it is better absorbed in a full stomach. The drug should be given immediately after grain meal.

Adverse effects: Include blisters on the nose and mouth, skin rash, hives, diarrhea, colic, and seizures.

2. **Nitazoxanide (Navigaror®):** It is a nitrothiazolyl-salicylamide derivative, which is a light yellow powder and lipophilic.

Mechanism of action: It is metabolized into a toxic-free radical from the “nitro” group, which blocks cellular respiration of protozoans.

Therapeutic uses: 32% nitazoxanide paste is used orally for the treatment of EPM. During days 1-5, 25 mg/kg; and days 6-28, 50 mg/kg.

Pharmacokinetics: following oral administration in horses, nitazoxanide is absorbed. Since it is a lipophilic drug, it is better absorbed on a full stomach. The drug should be given immediately after grain meal. The drug is metabolized into acetyl-nitazoxanide and acetyl-nitazoxanide glucuronide and eliminated in 24 hours in the urine, bile, and feces.

Adverse effects: they include GI disturbances (anorexia, diarrhea, colic) enterocolitis, fever, and anaphylaxis (laminitis and edema).

Contraindications: It should not be administered to horses that are < 1 year old; sick or debilitated for other reasons including hepatic and renal disorders.

3. **Metronidazole (Flagyl):** It is antiprotozoal and antibacterial agent and it is a lipophilic drug.

Mechanism of action: disruption of the DNA synthesis in the protozoans and bacteria.

Therapeutic uses: Metronidazole is a broad-spectrum antiprotozoal drug that is effective against *giardia*, *histomonas*, *babesia*, *trichomonas*, and *ameba*.

Pharmacokinetics: oral absorption is enhanced when the drug is given with food due to increased bile secretion that helps dissolve metronidazole. It is rapidly and widely distributed after oral absorption, because it is highly lipophilic. It is metabolized by hydroxylation and conjugation in the liver. Both metabolites and parent drug are eliminated in the urine and feces in 24 hours.

Adverse effects: High doses of metronidazole or prolonged administration may induce lethargy, weakness, ataxia, rigidity, anorexia, vomiting, diarrhea, reversible leukopenia, and hepatotoxicity.

Other drugs for treatment of giardiasis: include Albendazole and fenbendazole. These drugs are administered orally at 25 mg/kg every 12 hours for 2 days. Albendazole may be toxic to liver and bone marrow and is a teratogen.

Drugs for treatment of toxoplasmosis:

1. *Trimethoprim-sulfadiazine*
2. *Pyrimethamine*
3. *Clindamycin*

Drugs for the treatment of cryptosporidiosis

1. **Paromomycin (Humatin®):** It is aminoglycoside for extra-label use. It is administered to prevent and treat cryptosporidiosis at 50 mg/kg, PO, twice a day for 10 days. It has minimal absorption after oral ingestion because it is an aminoglycoside. It can induce vomiting, diarrhea, colic, renal toxicity, and deafness as signs of toxicity.
2. **Azithromycin (Zithromax®)**
3. **Nitazocanide**

Drug for treatment of babesiosis:

1. Imidocarb (Imizol®): It is a diamine derivative

Mechanism of action: Imidocarb binds to DNA and interfere with parasite DNA replication.

Therapeutic uses:

Dogs: Imidocarb is effective against *Babesia canis* when given at as single dose of 6.6 mg/kg IM or SC.

Horses: Imidocarb can eliminate equine babesia (*B. caballi*) when given 1-2 mg/kg, twice during a 24 hours period.

Pharmacokinetics: it rapidly absorbed from injection site. It is excreted mainly into urine and feces as unchanged drug.

Adverse effects: Common signs are pain during injection and parasympathetic stimulation such as salivation, nasal drip, or brief episode of vomiting. Atropine sulfate can be used to control the signs of parasympathetic stimulation. Since it is a teratogenic, it should not be used in pregnant animals.