
بسم الله الرحمن الرحيم

CHEMOTHERAPY OF ENDOPARASITIC DISEASE

Presented by:

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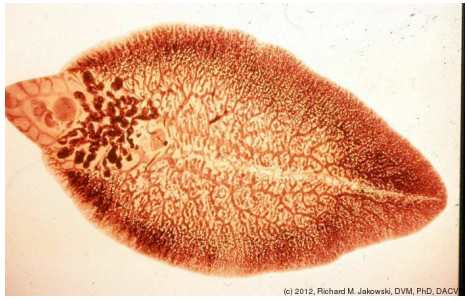
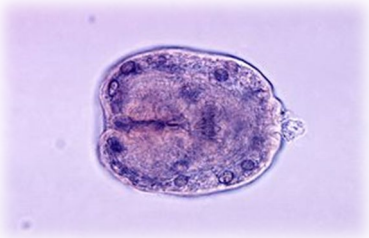
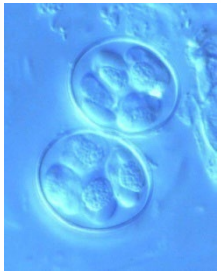
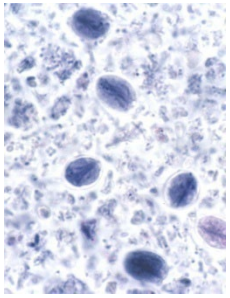
Antiparasitic drugs

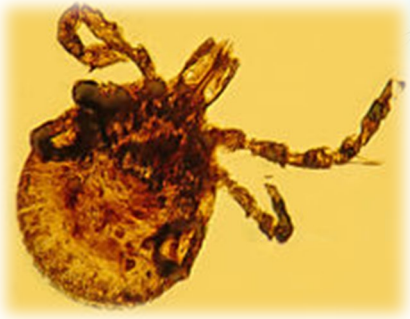
- Endoparasite
  - Anthelminthic
    - Antinematodal
    - Anticestodal
    - Antitrematodal
  - Antiprotozoal











overview

- Anthelmintics are used in all animal species and man
- The economic importance of helminth infections in pet
  - Public health
- Factors resonsible for therapeutic failure
  - Inadequate integration between management strategies and chemotherapy
  - Incorrect use of anthelmintic drug: insufficient pharmacology
  - Several host-related factors: pharmacikinetic modifications
  - Resistance in live stock(sheep and goat): many compound with common mode of action

Antinematodals

Benzimidazole

Imidazothiazole

Tetrahydropyrimidine

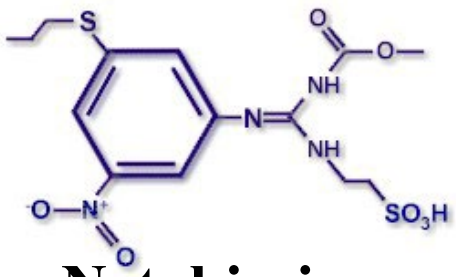
Organophosphate

Heterocyclic compounds

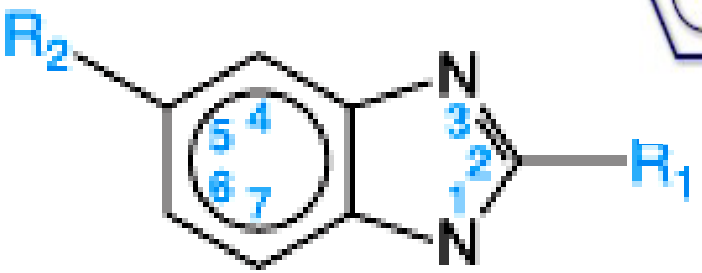
Heartworm adaulticides

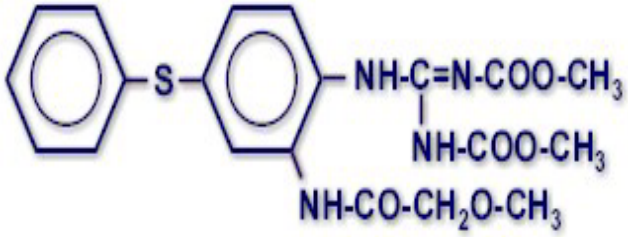
Benzimidazoles

- Probenzimidazole(pro-BZD): Febantel(FBT), Netobimin(NTB)
- Benzimidazole(BZD)
  - Thiazolyl: Thiabendazole(TBZ), Combendazole
  - **Methylcarbamate:** Mebendazole(MBZ), Albendazole(ABZ), Flubendazole(FLBZ), oxibendazole(OBZ), Albendazole sulphoxide(ABZSO)/Ricobendazole(RBZ), Fenbendazole(FBZ), Oxfendazole(OFZ)
  - Halogenated thiol: Triclabendazole
- SAR

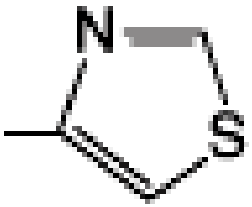
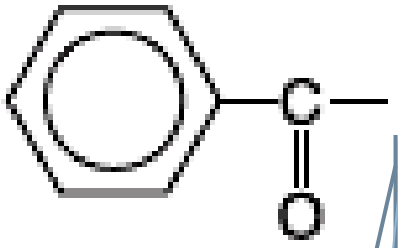
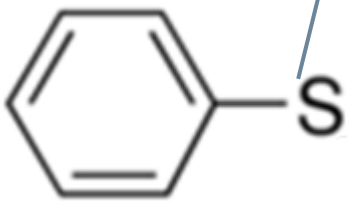


Netobimin





Febantel

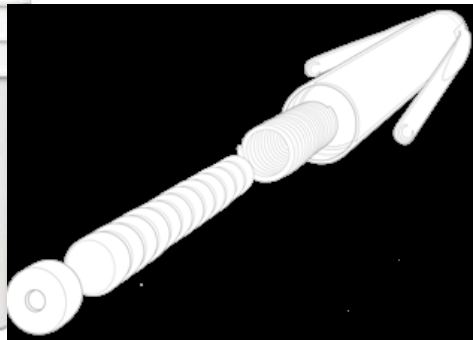
R_1	R_2	Derivative
	H—	Thiabendazole
—$NHCO_2CH_3$		Mebendazole
—$NHCO_2CH_3$	$CH_3CH_2CH_2S$—	Albendazole
—$NHCO_2CH_3$		Fenbendazole

Potent microtubule inhibitiry effect

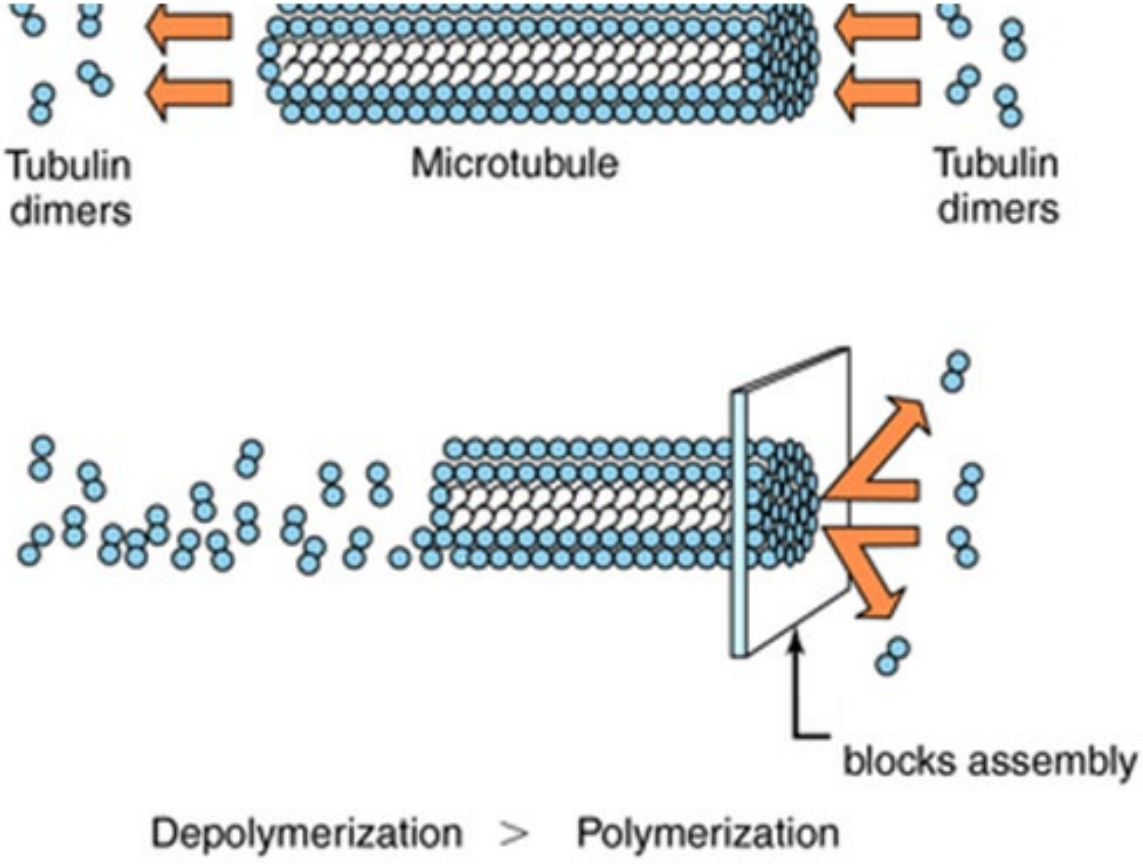
Larval stages of GI nematodes and lung worm

Cont…

- Advantages: safety, spectrum, larval stages
- Ruminant: ABZ, FBZ, and sulphoxide derivatives
- Horse: FBZ, OFZ
- Companion: FBT, FBZ, and MBZ
- Poultry and pigs: FBZ, FLBZ



Pharmacodynamic



- Selectivity: dissociation rate between host and parasite

Pharmacokinetics

- Low water solubility in methylcarbamates (limitation for formulation)⟶dissolution rate⟶rate and extent of absorption
  - Compared to TBZ
- Suspension(poor/erratic GI absorption), paste, granule, tablet

Pharmacokinetics

- Dog
  - MDZ is poorly absorbed after oral administration in dog
    - Multiple treatment
    - Lack of efficacy against lung parasites
  - Higher efficacy by increasing treatments rather than increasing dose in FBZ
  - FBZ plasma concentration is higher with it's administration in food
- Poultry:
  - FBZ is metabolized to OFZ(main) and $FBZSO_2$ earlier than ruminant
  - ABZ: ABZSO
  - FLBZ: H&R FLBZ

Drug transfer into target parasite

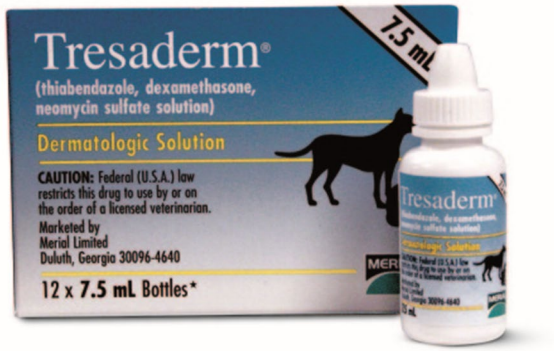
- Transcurticular diffusion is the predominant pathway for the entry anthelmintic drugs
  - Difference between nematode(cuticule) and cestode/trematode (tegument)
  - Lipophilicity of drug: ABZ /ABZSO, FBZ/OFZ, MBZ/TBZ

Anthelmintic Spectrum

- Methyl carbamate
  - Nematodes
    - GI
    - Lung
    - Activity against egg, immature and mature stages
  - Tapeworm
  - Trematode
- Thiazolyl has narrower spectrum than the previous one
- Halogenated thiol
  - All stages of *Fasciola hepatica*

TBZ

- Treat and control of GI round worms in horses, cattle, sheep, and goats
- Control of lungworms in sheep
- Associated with piperazine to increase efficacy against ascarids and immature oxyurus in horse



Externa otitis

Ricobendazole

- Suspension in cattle and sheep
- Europe: for the control of ascarids and capillarid in pheasants

FBT

- Suspension, paste or tablet for dogs and cats
- Dogs and cats required a 3day perioud of treatment
- Spectrum similar to FBZ and OFZ

FBZ

- Presents ovicidal activity
- Has antigiardial activity dog
- FDA approved for zoo and wildlife animals

MBZ

- Is administered orally to dog, cat, game birds and poultry
- Formulations: premix, paste, tablet, granule, and drench

FLBZ

- Tablet, paste, pellets, and premix in chikens, turkeys, and game birds
- Has ovicidal activity

Route of administration and Formulations

- Dog and cat: Tablet
- Poultry: Powder
- Methods of drug delivery:
  - incorporation into feed blocks, inclusion in drinking water(no direct control),
  - controled-release device or bolus (drug resistance)
- Drug combination may be a practical approach to delay the development of resistance
  - ABZ/levamisole, FBZ/levamisole, Ivermectin/ABZ

Toxicity

- Remarkable overall safety of BZD
- Teratogens: cambendazole, OFZ, FBT, and ABZ in 4times recommended dose
  - No use in early stages of pregnancy
  - Most sensitive: sheep
  - Occur at dosages much lower than acute toxicity
  - FBT do not recommended in pregnant dog and cat
- TBZ anemia in dog

Imidazothiazoles

- Tetramisole
  - S(-): L ⟶ anthelmintic activity
  - R(+): D
- Levamisole dose is half that of tetramizole
- Butamisole hydrochloride used as injectable anthelmintic to control of whipworm(*Trichuris*) and hookworm (*anchylostoma*) in dogs

levamisole

- Formulation flexibility: oral(drench, premix, solution, tablet), parentral, and topical(pour-on)
- Has hydrochloride (injection[IM,SC], drench) and phosphate salts(injection[IM,SC])
- Mode of action: cholinergic agonist at synaptic and extracynaptic nicotinic ACh receptors
- Transcuticular diffusion

Levamisole

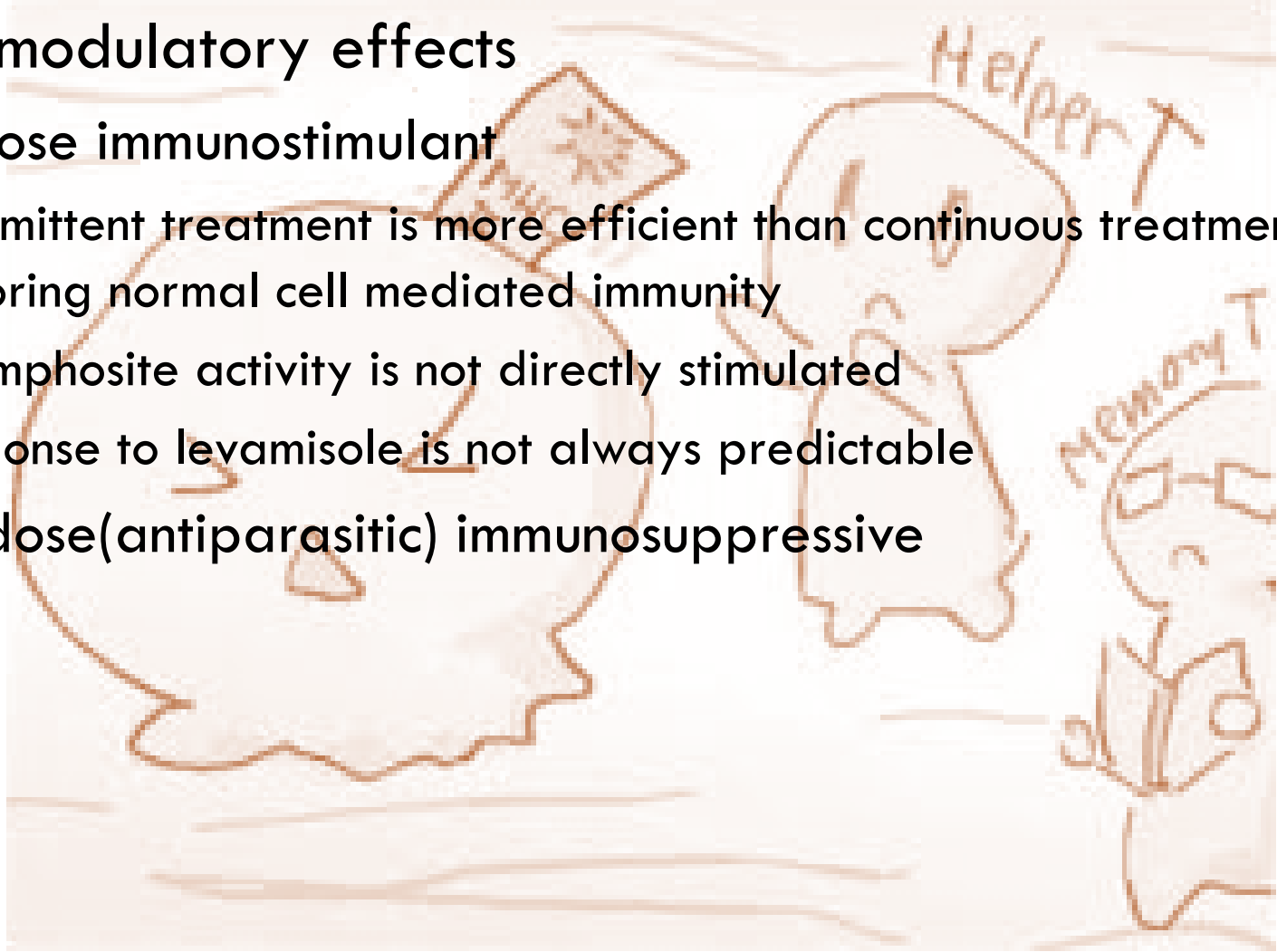
- Pharmacokinetic
  - Tmax: injection>oral>topical
  - F: SC>oral>topical
  - Oral absorption in fasted dog is higher than feed
  - Concentration dependent
  - Wide distribution: muscle, fat, kidney, **liver**
  - Is fast depleted (**urine**&feces) from the animal body and tissue residues of the drug are not appreciable
- Spectrum: mature stages of major GI nematodes, mature and larval stages of lungworm, dirofilaria immitis in dogs
  - Is not effective agianst canine whipworm

Levamisole

- Poultry
  - Inclusion to drinking water
- Dog and cat
  - Tablet and solution
- Acceptable safety and spectrum activity coupled with very low cost → useful nematocidial

Levamisole

- Immunomodulatory effects
  - Low dose immunostimulant
    - Intermittent treatment is more efficient than continuous treatment in restoring normal cell mediated immunity
    - B-lymphosite activity is not directly stimulated
    - Response to levamisole is not always predictable
  - High dose(antiparasitic) immunosuppressive



Levamisole

- Safety and toxicity
  - Muscarinic and Nicotinic effects (cholinestrase inhibition)
  - Parenteral is more dangerous than oral and topical
    - IV is never recommended
  - Chickens tolerate levamisole very well
- Drug interaction with organophosphate, carbamate, pyrantel, morantel

Macrocyclic Lactones

- Avermectins
  - Bind to Glutamate receptors, certain chloride channels in the parasite nerve and muscle cells, causing paralysis (unable to depolarize muscle – unable to contract) and death of the parasite
  - The representative of this group is **ivermectin,** used for a wide variety of endo- and ectoparasites
    - May be combined with other antiparasitic agents to broaden its spectrum of activity
    - Heartgard Plus® (contains ivermectin and pyrantel pamoate)
  - Oral (**Heartgard®**) and parenteral forms (**Ivomec®**) available
  - Used for heartworm prevention
  - **Collies (collie like breeds: Shetland sheepdogs, Australian shepherds) are ivermectin sensitive**
  - Another example in this group is **moxidectin (ProHeart-6®, Advantage Multi®)**
  - **Not** effective against cestodes or trematodes

Macrocyclic Lactones

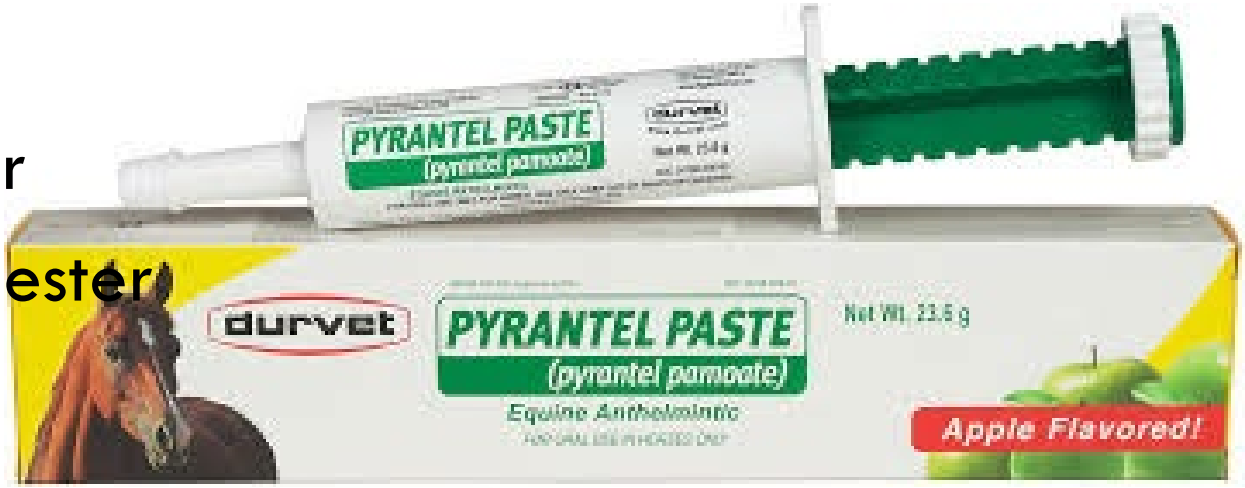
- Selamectin
  - Local in dog and cat
  - Safer than ivermectin in dog

Macrocyclic Lactones

- Milbemycin
  - Nematode and haert worm in dog

Tetrahydropyrimidines

- Pyrantel
- Morantel metylester
- Oxantel oxyphenolester



Pyrantel

- Tartrate(more water soluble than pa.), citrate, and pamoate(embonate, water and alcohol insoluble)
- Mode of action: cholinergic agonist at synaptic and extracynaptic nicotinic acetylcholine receptors
  - 100 times more potent than Ach
  - Oxantel has higher efficacy against *Trichuris*
- Pharmacokinetic
  - Oral absorption tartrate salt is higher than pamoate salt
  - Fecal excretion
    - Exception: dog

Pyrantel

- Dog
  - Pamote suspension and chewable tablet
  - Coupled with praziquantel and febantel
  - Combined with ivermectin
- Cat
  - Coupled with praziquantel
  - Is used after feed

Pyrantel

- Spectrum:
  - Dog: ascarids (*Toxocara canis*, *T. leonina*), hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), and stomach worm (*Physaloptera*)
  - Cat and kitten similar to dog
  - Has been used in pet birds
- Safety
  - Is not recommended for use in severly debilitated animals
  - Emesis may possibly occur in small animals
  - Morantel tartrate is safer than pyrantel tartrate

S(-) LEVAMISOLE		PYRANTEL MORANTEL
Nicotinic receptor agonism	MODE OF ACTION	Nicotinic receptor agonism
Lung and GI nematodes (mainly adult stages)	ANTHELMINTIC SPECTRUM	GI nematodes (narrow, adult stages Equine tapeworms (pyrantel)
Side-resistance with pyrantel and morantel	ANTHELMINTIC RESISTANCE	Side-resistance with levamisole
Rapid absorption (injectable) Limited absorption (oral, topical) Fast elimination	PHARMACOKINETICS	Poor GI absorption (ruminants) Good GI absorption (dog, pig)
Subcutaneous, Oral, Topical	ROUTES OF ADMINISTRATION	Oral (all species) Slow release bolus (cattle)
Hydrochloride, phosphate	FORMULATIONS	Pamoate, tartrate
Narrow safety margin (do not use in horses)	TOXICITY	Good safety margin

Heterocyclic Compounds

- Phenothiazine
- Piperazine
- Diethylcarbamazine citrate

Piperazine

- Efficacy
  - Good: ascarids in domestic animals
  - Moderate: pinworm
  - Zero to variable: other helminths
  - Is not active against immature
- Low cost and wide safety: worldwide use
- Relatively unstable: formulated as different salt such as adipate, citrate, phosphate, hexahydrate, and sulphate that their activity is lower than base
- Mode of action
  - **Curare like effect**
  - Agonist of chlor ligand gated channels(GABA and glutamate)

Narrow spectrum
Adult more suseptible
Immature adult and lumen larvae suseptibl
Larval stages relatively insuseptible

Piperazine

- Contraindications: Chronic liver & kidney disease, gastrointestinal hypomotility
- Caution: Seizure disorders
- Adverse Effects: Unlikely, but diarrhea, emesis, or ataxia possible

Diethylcarbamazine(DEC)

- Tablets or chewables
- Heartworm disease prophylaxis should be administered daily throughout the mosquito vector season and continued for 2 months following
- In zoo animals susceptible to heartworm
- In cats, may help alleviate the course (preventing lymphoma development) of FeLV infection
- Mode of action: inhibits cyclic peroxide generation from arachidonic acid breakdown
  - Has immunomodulatory effects via an unknown mechanism
- Is contraindicated in dogs with adult filaria, as a shock-like reaction can occur(0.3-5%)
- Has been reported to cause infertility problems in male dogs

PIPERAZINE (MW 86.1 Kda)		DIETHYLCARBAMAZINE (MW 391.4 Kda)
GABA agonism. Flaccid paralysis	**MODE OF ACTION**	Inhibits cyclic peroxide generation from arachidonic acid breakdown
Narrow nematodicidal (mainly ascarids)	**ANTIPARASITIC SPECTRUM**	Only microfilaria in dogs
Horses, dogs, cats, pigs and poultry	**TARGET SPECIES**	Dogs
Formulated as various salts. Dogs-Cats 45-65 mg/kg, horse-swine 110 mg/kg, Chicken 32 mg/kg.	**FORMULATIONS - DOSES**	Tablets (6.6 mg/kg) Powder (2.5 mg/kg)

Organophosphate

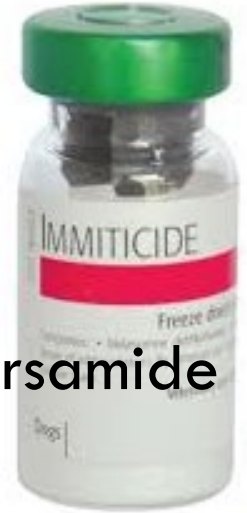
- Dichlorvos, trichlorfon, haloxone, coumaphos, naphthalophos, and crufomate
- Dichlorvos
  - Is useful in control equine bot flies
  - Abomasal and small intestine nematodes

Heartworm adulticide

- Thiacetarsamide sodium
  - Recommended to evaluate kidney and liver function before dosing
  - Mode of action: persumably du to cell glycolysis
  - Treatment
    - Heartworm: adulticie
    - Chronic fatigue syndrom associated with *bacteremia Staph. SPP*
  - Toxicity
    - Vommiting, icterus, and orange colored urine
    - Antidote: dimercaprol

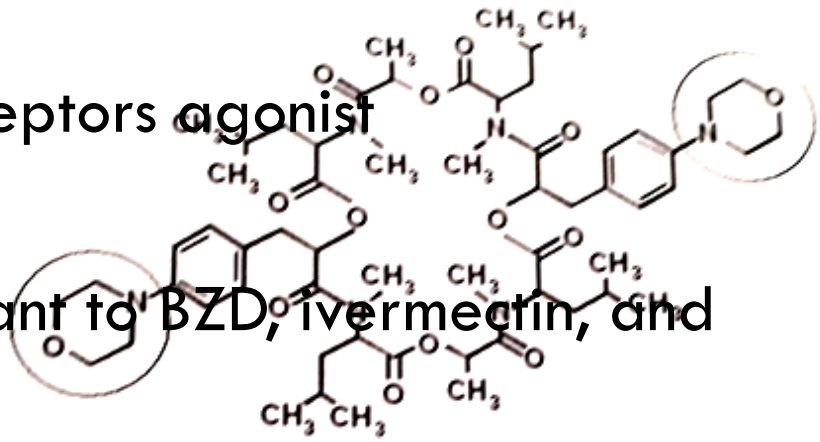
Heartworm adulticide

- Melarsomine
  - FDA approval for dogs under hospital setting
  - Isn't binded to RBC, unlike thiacetarsamide
  - Arsenic plasma level is higher and longer than thiacetarsamide
  - Active against immature and mature dirofilaria
  - Safer than thiacetarsamide
  - Toxicity
    - Pain, swelling, and tenderness in site of injection, couphing, gagging, fever, depression, lung congestion and vomitting
    - Antidote: dimercaprol



Novel drugs

- Nitazoxamide
  - Nematode, trematode, cestode, protozoa, bacteria
  - Efficacy patterns are too low
- Emodepside
  - Mode of action: latrophilinlike reeptors agonist
  - Broad nematocidal activity
  - Activity against nematodes resistant to BZD, ivermectin, and levamisole
  - Commercially available for cats



Anticestodes

Bunamidine

Niclosamide

Praziquantel

Epsirantel

Bunamidine

- Disrupts tegument and reduces glucose uptake and subtegumental tissue destroyed by host's digestive enzyme
- Tablet(hydrochloride): companion
  - Is indicated for treatment of
    - *Spirometra spp*, *Mesocestoides spp*, *Taenia spp* and Diphyllobothrium spp
    - *E. granulosus*: immature(85.9-98.8%), mature(100%)
  - Dissolution of tablet in fasted animal is improved and contact of drug with parasite enhance that result in increase of efficacy
- Drug is safe because oral absorption is low and is inacivated in liver
  - Dissolved tablet cant cause liver damage and ventricular fibrilation?
- Emesis and diarrhea most frequent adverse effect

Niclosamide

- High effective against most of the tapeworm species in companion animal
  - Poor efficacy against *Dipylidium* and E. *granulosus*
- Mode of action: inhibits glucose uptake, oxidative phosphorylation, and anaerobic metabolism in the tapeworm
- Tablet(companion animal), suspension(ruminant)
- In fasted animal increases efficacy
- Well-known saftey because low absorption and rapid metabolism

Praziquantel

- Active against Adult & larval stages of cestodes and FDA-approved for
  - *Dipylidium caninum*, *Taenia pisiformis*, and *Echinococcus granulosis(unique)* in dogs
  - *Dipylidium caninum* and *Taenia taeniaeformis* in cats
- Fasting is not required nor recommended before dosing
- A single dose is usually effective, but measures should be taken to prevent reinfection, particularly against *D. caninum*
- In humans: schistosomiasis, other trematodes (lung, liver, intestinal flukes) and tapeworms

Praziquantel

- Combination of febantel and praziquantel is for GI nematode and cestode in young dogs
- Combination of praziquantel, pyrantel and oxantel is marketed as a broad spectrum dewormer for dog and cat
- Combination products(gel, paste) containing ivermectin plus praziquantel in the treatment of equine GI cestode and trematode
- Praziquantel has been used in birds
- Praziquantel has a wide margin of safety

Praziquantel

- Exact mechanism of action has not been determined, but it may be the result of interacting with phospholipids in the integument causing ion fluxes of sodium, potassium and calcium
- Focal vacuolization of the integument follows and the parasite is phagocytized
- In schistosomes and trematodes, directly kills the parasite, possibly by increasing calcium ion flux into the worm

Praziquantel

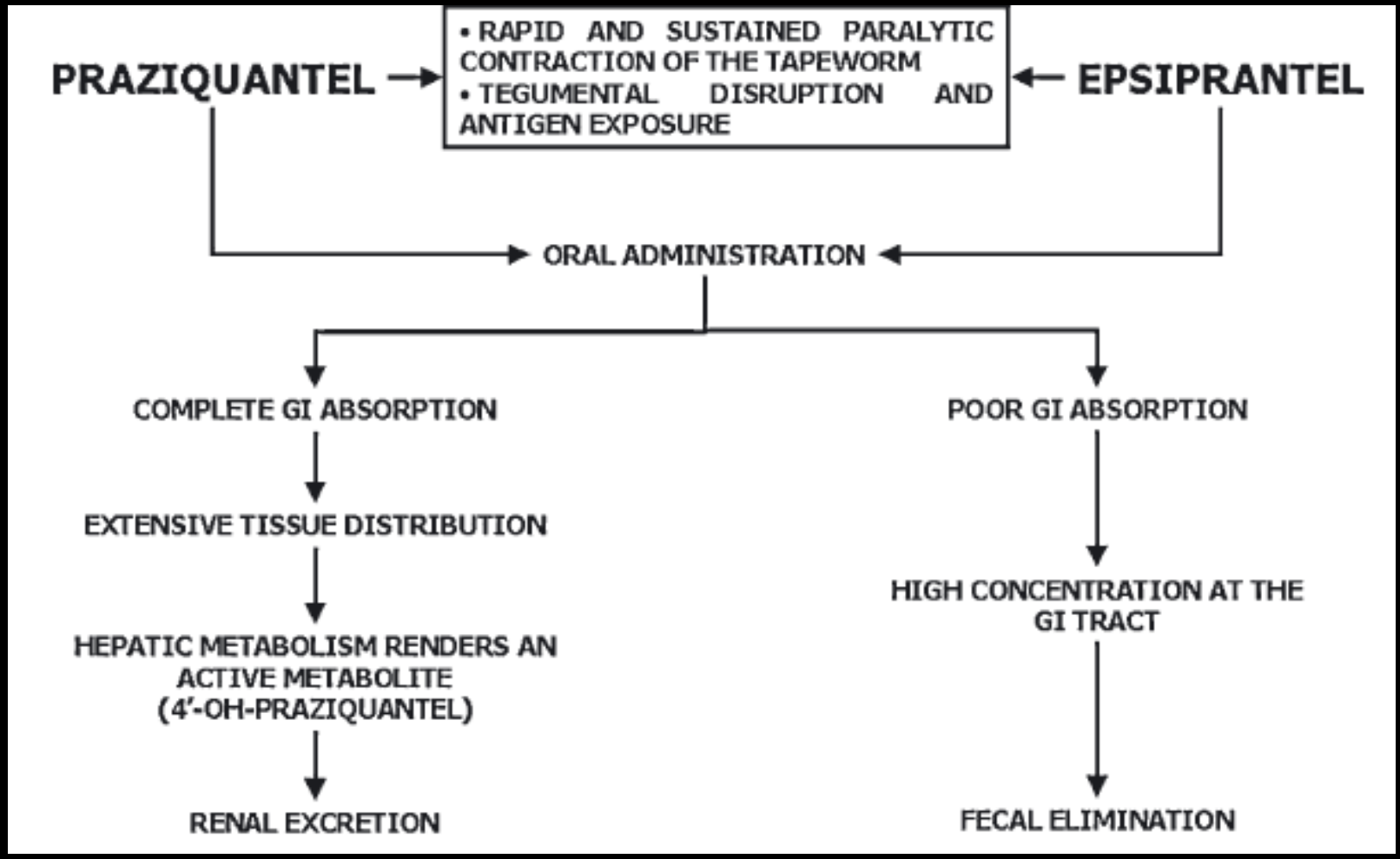
- Pharmacokinetic
  - Is rapidly and nearly completely absorbed after oral administration, but there is a significant first-pass effect
  - Is distributed throughout the body; It crosses the intestinal wall and across the blood-brain barrier into the CNS
  - Is metabolized in the liver via CYP3A enzymes to metabolites of unknown activity
  - It is excreted primarily in the urine; elimination half-life is approximately 3 hours in the dog
  - In dogs, orally administered grapefruit juice can increase the AUC by 150–200%

Praziquantel

- Is not recommends using praziquantel in puppies less than 4 weeks old or in kittens less than 6 weeks old
  - A combination product containing praziquantel and febantel is FDA-approved for use in puppies and kittens of all ages
- Adverse effects
  - Oral
    - In dogs: anorexia, vomiting, lethargy, or diarrhea (<5%)
    - In cats: salivation and diarrhea (<2%)
  - Injection
    - Dogs: pain at the injection site, vomiting, drowsiness, and/or a staggering gait
    - Cats (9.4%): diarrhea, weakness, vomiting, salivation, sleepiness, transient anorexia, and/or pain at the injection site

Epsirantel

- Effetive against common cestodes: *D. caninum*, *T. pisiformis*, *E. granulosus*, *T. taeniaformis*
- Only formulated for dogs&cats
- Oral absorption is poor
  - So is used against intestinal cestode and is safe drug
- Emesis is the most common side effect and occur in prolonged treatment


PRAZIQUANTEL
• RAPID AND SUSTAINED PARALYTIC CONTRACTION OF THE TAPEWORM
• TEGUMENTAL DISRUPTION AND ANTIGEN EXPOSURE
EPSIPRANTEL
ORAL ADMINISTRATION
COMPLETE GI ABSORPTION
EXTENSIVE TISSUE DISTRIBUTION
HEPATIC METABOLISM RENDERS AN ACTIVE METABOLITE (4'-OH-PRAZIQUANTEL)
RENAL EXCRETION
POOR GI ABSORPTION
HIGH CONCENTRATION AT THE GI TRACT
FECAL ELIMINATION

Antitrematode

Nitrophenolic compounds

Salicylanilides

BZD

Phenoxyalkanes

Antiprotozoal

Anticoccidial

Diclazuril

- Is a slightly yellowish to beige powder, and it is almost insoluble in water
- Mode of action: is effective against schizonts and gametes by inhibiting nuclear division
- It is used as a feed additive to prevent coccidiosis in broilers
  - Since it is effective against later stages of coccidia, it has potential to be used for treating outbreaks of coccidiosis
- It could be used in an extra-label manner to treat mammalian coccidiosis, EPM, toxoplasmosis, and controling the clinical signs of intestinal ciccidiosis in rabbits

Toltrazuril

- Mode of action: Toltrazuril and ponazuril are effective against schizonts and gametes by inhibiting nuclear division
  - Canine Hepatozoonosis: relapsed and eventually died

Metronidazole

- Mode of action. disrupts DNA synthesis in protozoans and bacteria
- Is a broad-spectrum antiprotozoal drug that is effective against *giardia, histomonas, babesia, trichomonas, and ameba. It is approved* as a human drug, and has been used largely in small animals
- Pharmacokinetics
  - Absorption. The oral bioavailability of metronidazole in animals varies 50–100%. If given in food, absorption is enhanced, attributable to increased bile secretion that helps dissolve metronidazole. Peak blood levels occur within 1 hour of administration

Metronidazole

- Adverse effects: High doses of metronidazole or prolonged administration may induce lethargy, weakness, ataxia, rigidity, anorexia, vomiting, diarrhea, reversible leukopenia, and hepatotoxicity
  - Because metronidazole affects DNA synthesis, it may have teratogenic and carcinogenic effects
- Metronidazole benzoate

Other drugs

- Tinidazole: *Trichomonas in cat, Giardia in dog and cat*
- Ronidazole: *Trichomonas* in cat and pigeon
- Albendazole and fenbendazole administered orally in giardiasis dogs, and cats

Drugs for treatment of toxoplasmosis

- Trimethoprim-sulfadiazine
- Pyrimethamine
- Clindamycin

Drugs for the treatment of cryptosporidiosis

- Paromomycin is an aminoglycoside for extra-label use
  - It can prevent and treat cryptosporidiosis at 50 mg/kg, PO, twice a day for 10 days.
  - Pharmacokinetics: No information is available for animals. However, GI absorption after oral administration is minimal, since it is an aminoglycoside.
  - Adverse effects: induces vomiting, diarrhea, colic, renal toxicity, and deafness
- Azithromycin is a macrolide and inhibits protein synthesis
- Nitazoxanide is used in humans for the treatment of cryptosporidiosis

Babesiosis

- Diminazene
  - Dog
- Pentamidine
  - Dog
- Phenamidine
  - Dog
- Amicarbalide

- Chlortetracycline
  - Cat
- Doxycycline
  - Dog

Babesiosis

- Imidocarb
  - Dog
  - Adverse effects: commonly seen are pain during injection and signs of parasympathetic stimulation such as salivation, nasal drip, or brief episodes of vomiting. Other effects seen less frequently are panting, restlessness, diarrhea, and injection site inflammation lasting one to several days. Atropine sulfate can be used to control the signs of parasympathetic stimulation.
    - Imidocarb is a teratogen and carcinogen, since it affects DNA synthesis. Do not use in pregnant animals.
- Atovaquone with azitromycin for elimination of babesia gibsoni in dogs