ANTHELMINTICS

Antinematodal drugs

Anticestodal drugs

Antitrematodal drugs

Anthelmintics

- Drugs which are used to either kill (vermicide) or expel (vermifuge) the parasitic worms or helminths which inhabit the GIT, and other tissues and organs of the body

- Properties of an Ideal Anthelmintics
  - Broad-spectrum of activity (against nematodes, cestodes and trematodes)
  - Wide safety margin
  - Selective toxicity, should not interfere with normal functions of host
  - Effective against adult and juvenile stages of helminths
  - Residues - Minimal withdrawal period
  - Easy to administer to large number of animals in herd or flock
  - Stable, economical
  - Compatible with food and other compounds

Anti-Nematodal Drugs

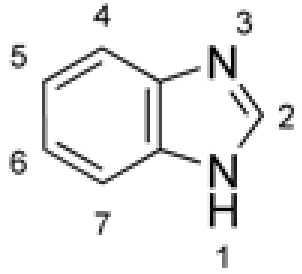
- Selective toxicity of drugs is by targeting the special metabolic processes of the worm or by inherent PK properties – to expose worms with high conc.
- Classification
  1. Benzimidazoles
     - Benzimidazoles – Tiabendazole, Albendazole, Fenbendazole, etc.
     - Pro-benzimidazoles – Febantel, Netobimin and thiopanate
  2. Macrocyclic lactones / Antibiotics
     - Avermectins – ivermectin, doramectin, eprinomectin, etc.
     - Milbemycins – Milbemycin oxime and moxidectin
  3. Imidazothiazoles – Tetramisole, levamisole and butamisole
  4. Tetrahydropirimidines – Pyrantel, Morantel and Oxantel
  5. OPC – dichlorvos, metrifonate, coumaphos, haloxon, etc

Anti-Nematodal Drugs

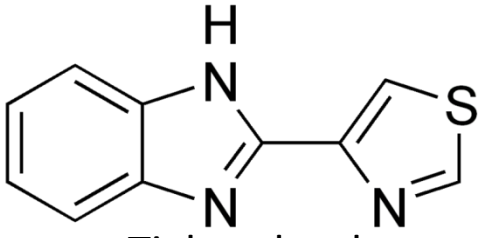
- Classification
  6. Piperazines – Piperazine and diethylcarbamazine
  7. Arsenicals – thiacetarsamide, melarsomine, glycobiarsol, arsenamide
  8. Substituted Phenols and Salicylanilides – disophenol, closantel, etc.
  9. Octadepsipeptides – emodepside
  10. Aminoacetonitrile – monepantel
  11. Miscellaneous drugs
      - Phenothiazine, Tetrachloroethylene, N-butyl chloride, Toluene, Thenium closylate, Phthalofyne, Dithiazanine iodide and Hygromycin B

Anti-Nematodal Drugs

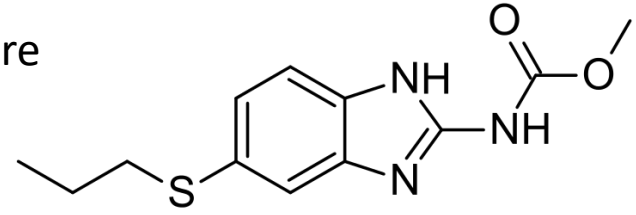
- Benzimidazoles:
  - Broad spectrum
  - Wide margin of safety
  - High degree of efficacy
  - Sparingly soluble in water
  - Given orally as suspension, paste or powder or intraruminal injection
  - Chemistry: benzene and imidazole ring,
    - Modifications at 2 and/or 5 positions – different drugs



Benzimidazole Ring structure



Tiabendazole

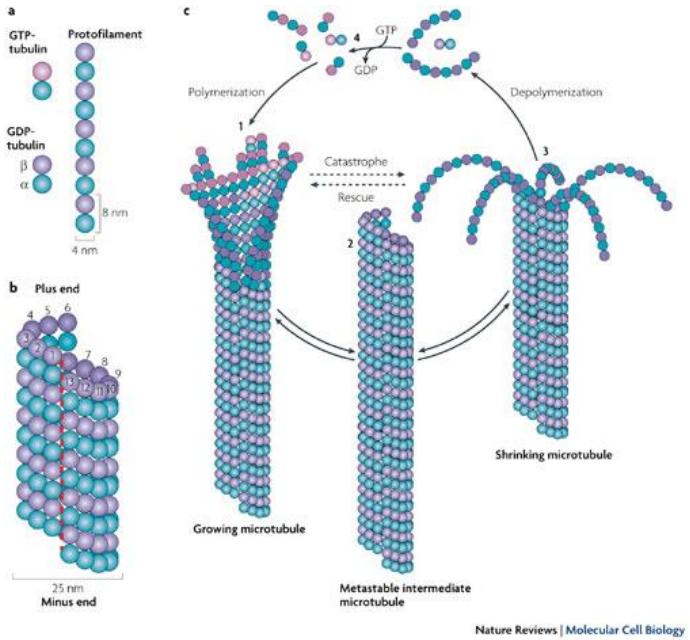


Albendazole

Anti-Nematodal Drugs

Benzimidazoles:

- MoA: Vermicidal
  - Binds to β-tubulin – inhibits its polymerization or assembly into microtubules
    - Continual depolymerization on the other end - complete breakdown
      - Disrupts the integrity and the transport function
      - Blocks cell division
    - Selective binding to parasite β-tubulin rather than mammalian tubulin



Anti-Nematodal Drugs

Benzimidazoles:

- MoA: Vermicidal
  - Inhibition of mitochondrial fumarate reductase enzyme
  - Block glucose transport and uncoupling of oxidative phosphorylation
  - Induce sterility in parasite by inhibition of egg production

- Antiparasitic action depends on their contact time rather than dose

- Resistance due to altered β-tubulin with low affinity for binding of drugs

Benzimidazoles

Tiabendazole (or Thiabendazole)

- First benzimidazole introduced in 1961
- Active against nematodes, fungi and mites
- Also has anti-inflammatory, antipyretic and analgesic actions
- Broad spectrum anthelmintic – all major GI nematodes of sheep, goats, cattle and horses. Swine – *Ascaris suum, Strongyloides ransomi*. Dogs – *Toxocara canis, strongyloides, Filaroides* spp.
- Less effective against lungworm and whipworm
- Effective against mature worms
- PK:
  - rapid absorption by oral route, Tmax – 2-7 h,
  - distributed to all body tissues,
  - metabolised to 5-hydroxybenzimidazole,
  - excreted in conjugated form (80%) and feces (5%),
  - Complete excretion occurs within 5 days of single oral administration

Benzimidazoles

Tiabendazole (or Thiabendazole)

- Adverse effects: wide safety margin, Diarrhoea, vomiting, hair loss, lethargy
  - Dachshunds – susceptible to the adverse effects of thiabendazole
- Safe during pregnancy
- Competes with methylxanthines for metabolism – should be avoided
- Clinical uses
  - Doses may be repeated in dogs and pigs
  - Single dose is effective in ruminants and horses
  - Zero day withdrawal period
- Dose:
  - Dogs: 50 mg/kg, OD – 3 days, repeat after one month
  - Ruminants, Swine, Horses : 50-100 mg/kg, PO single dose
  - Poultry 250-500 mg/kg, PO, repeat after 14 days, or 0.5% in feed for 10 days

Benzimidazoles

Albendazole

- Active against nematodes , cestodes and trematodes (broad spectrum)
- Larvicidal – hydatid cysts, cysticercosis, ascariasis and hookworms
- Ovicidal – ascariasis, ancylostomiasis and trichuriasis
- PK:
  - Oral F>50%, First pass metabolism – active sulphoxide metabolite – main drug
  - Distributed widely incl. CNS
  - Excreted in urine
- Well tolerated at recommended dose, Teratogenic
- Used in empty stomach against intraluminal parasite, with fatty meal for tissue parasites
- Dose:
  - For nematodes, trematodes and cestodes; Ruminants, Swine 5-10 mg/kg, PO
    - Horse: 25 mg/kg, PO, BID for 5 days
  - For Filaroides; dogs : 25-50 mg/kg, PO – BID for 5 days repeat after 21 days
  - For *Paragonimus kellicotti* infection; cats: 25 mg/kg, PO-BID for 10-21 days

Benzimidazoles

Fenbendazole

- Broad spectrum anthelmintic
- Active against nematodes of farm, companion and zoo animals
- Used in bitches prior to whelping for the treatment of tissue dwelling larvae of *Toxocara canis*, *Ancylostoma caninum*
- PK:
  - Marginally absorbed, First pass metabolism – active sulphoxide metabolite (oxfendazole) and further oxidised to sulphone
  - Excreted in feces unchanged
  - In ruminants, undergo enterohepatic cycling – prolongs duration of action
- Cattle with heavy lungworm infection – allergic reaction due to release of antigens by dying parasites
- Exotic birds (doves and pigeons) and reptiles (vipers, turtles & tortoises) – toxicity – bone marrow suppression, intestinal crypt cell necrosis
- Withdrawal period – 14 days for meat, 72 hours for milk
- Dose:
  - Dogs & Cats: 50 mg/kg, PO – OD for 3 days
  - Ruminants, Swine and Horses : 5-10 mg/kg, PO - single dose
  - Birds : 10-15 mg/kg, PO – single dose, repeat in 10 days

Benzimidazoles

Mebendazole

- Broad spectrum anthelmintic
- Effective against lungworms, tape worms of sheep, dogs & cats, antifilarial
- PK:
  - Oral F <10%, fatty meal increase the absorption
- Embryotoxic and Teratogenic – not used in pregnant animals
- Not used in cattle
- Dose:
  - Dogs & Cats: 25-50 mg/kg, PO – BID for 5 days
  - Sheep, Horses and Poultry: 10 mg/kg, PO - single dose, 3 days (poultry)
  - Birds : 25 mg/kg, PO – BID, - 5 days

Benzimidazoles

Oxibendazole

- Broad spectrum anthelmintic
- Effective against GI roundworms or lungworms
- Usually given in horses (TI = 60x the recommended dose for horses)
- PK: Oral F <10%, fatty meal increase the absorption
- Dose:
  - Horse: 10 mg/kg, PO, SD (15 mg/kg for strongyloides)
  - Cattle, Sheep and Swine : 10-20 mg/kg, PO

Other benzimidazoles with similar effect

Oxfendazole – sulphoxide metabolite of fenbendazole, metabolism – fenbendazole and sulphone.

Cambendazole – narrow margin of safety

Flubendazole – poorly absorbed from oral route, less toxic

Parbendazole – embryotoxic and teratogenic

Benzimidazole - Prodrugs

Febantel

- Active metabolites – fenbendazole and oxibendazole
- Broad spectrum anthelmintic
- PK: readily absorbed from oral route, metabolised to active, Tmax – 6 -12, 12-24 h in sheep and cattle respectively
- Combination with Praziquantel in horse - GI disturbances, colic in horse (40x safety margin)
- Dose:
  - Horse: 6 mg/kg, PO, SD
  - Cattle, Sheep and Swine : 5-7.5 mg/kg, PO, SD
  - Pigeons – 30 mg/kg, PO
  - In combination with Praziquantel in Dogs & Cats
    - > 6months of age – 10 mg/kg (febantel) + 1 mg/kg (praziquantel)
    - < 6 months of age – 15 mg/kg (febantel) + 1.5 mg/kg (praziquantel)

Benzimidazole - Prodrugs

Netobimin

- Active metabolites – Albendazole
- Dose:
  - For roundworms and tapeworms; Cattle& Sheep : 7.5 mg/kg, PO, SD
  - For adult flukes, Cattle& Sheep : 20 mg/kg, PO

Thiophanate

- Pro-drug of lobendazole
- Active against roundworms of ruminants and pigs
- Very safe even at high doses
- Dose:
  - Cattle, Sheep & Goat : 50 mg/kg, PO-SD
  - Pigs: 5-12 mg/kg, PO – 14 days

Macrocyclic Lactones / Macrolides Endoectocides

- Antibiotics produced by Streptomyces spp.
- Active against mature and immature nematodes and external arthropods
- Two major groups – Avermectins and Milbemycins

Avermectins

- Isolated from *Streptomyces avermitilis*, mixture of four major components (A_{1a}, A_{2a}, $\mathbf{B_{1a}}$, B_{2a}) and four minor components (A_{1b}, A_{2b}, B_{1b}, B_{2b})
- No activity against Platyhelminths (Cestodes and Trematodes)
- Available drugs are Ivermectin, Abamectin, Doramectin, Eprinomectin and Selamectin
- MoA:
  - Bind to glutamate gated Cl^- channel – hyperpolarisation - results in paralysis and death
    - Disruption of reproductive function in ticks
  - Bind to GABA-gated Cl^- channel – hyperpolarisation (less important)
  - Selective toxicity – due to the absence of avermectin sensitive glutamate gated ion channels in mammals

Macrocyclic Lactones / Macrolides Endoectocides

Ivermectin

- Semi-synthetic derivative of avermectin
- Highly lipophilic
- Effective against nematodes like strongyles, ascarids, pinworm, hairworm, bots, lungworms, threadworms, heartworm
- Effective against ectoparasites like cattle grubs, sucking lice, mites and horn flies
- PK:
  - Oral F >90%, SC inj – better BA but slow
  - Highly lipophilic, well distributed except CNS. Collie breed of dogs – cross CNS – results in ivermectin toxicity
  - Metabolised by oxidation
  - Excreted in both unchanged or metabolised forms in the feces – degradation in soil is very slow – suppress the larvae of dung-breeding larvae
  - Long $t_{1/2}$- dogs- 2 days, cattle – 2-3 days, sheep – 2-7 days, swine -0.5 days

Macrocyclic Lactones / Macrolides Endoectocides

Ivermectin

- Adverse effects:
  - High safety margin (TI >30) in cattle
  - Hypersenstivity due to dead parasites in horse
  - Toxic in Collie breed due to the mutation in MDR1 –Pgp in BBB
    - Toxic signs include mydriasis, salivation, ataxia, tremors, paresis, stupor, recumbency and coma
    - Hypersensitivity due to dying microfilaria
  - Neonates are more susceptibile due to immature BBB
  - Antidote of ivermectin toxicity – Physostigmine – i/v route

- Contraindication
  - Not recommended in calves < 12 weeks, puppies < 6 weeks
  - Only SC or oral routes are recommended, should not be given in IV or IM
  - Only oral route for horse

Macrocyclic Lactones / Macrolides Endoectocides

Ivermectin

- Dose:
  - Dogs : 0.2 -0.3 mg/kg, SC or PO , q14d
  - Cats: 0.4 mg/kg, SC
  - Horses: 0.2 mg/kg, PO
  - Ruminants & Swine: 0.2 mg/kg SC or PO (sheep and goat)
  - Birds : 0.2 - 0.4 mg/kg, PO, IM or SC
  - For prevention of heartworm infection
    - Dogs: 0.006 mg/kg, PO, once monthly
    - Cats: 0.024 mg/kg, PO, every 30-45 days

Macrocyclic Lactones / Macrolides Endoectocides

Abamectin

- Isolated from fermentation product of *Streptomyces avermitilis*
- Active against nematodes and arthropods
- Slightly more toxic than ivermectin – lethargy, ataxia, tremors and/or coma
- Dose: Cattle: 0.2 mg/kg, SC

Doramectin

- Used in cattle, sheep and swine but not recommended in dogs due to high incidences of toxicity and fatality
- Dose: Cattle: 0.2 mg/kg, SC, 0.5 mg/kg, topical (pour-on formulation)
- Swine : 0.3 mg/kg, IM

Macrocyclic Lactones / Macrolides Endoectocides

Eprinomectin

- Applied topically, not recommended for oral or IV routes
- Tmax: 2-5 days, not metabolised, excreted unchanged in feces
- Cattle: 0.5 mg/kg, pour-on

Selamectin

- Used only topically
- $T_{1/2}$; dogs -11 days, cats -8 days
- Safe for use in dogs and cats, no adverse effects is reported in Collie dog
- Spot-on formulation – 6% or 12%
- Dogs & Cats: 6 mg/kg, topically, repeated after 30 days

Macrocyclic Lactones / Macrolides Endoectocides

Milbemycins

MoA is similar to Avermectin – Milbemycin oxime & Moxidectin

Milbemycin oxime

- Fermentation product of *Streptomyces hygroscopicus aureolacrimosus*
- Endoectocide, less potent than ivermectin for heartworm
- Effective against ectoparasites like cattle grubs, sucking lice, mites and horn flies
- PK: similar to ivermectin, administered orally – effective against D. immitis for 45 days
- Well tolerated in dogs and cats, non-toxic to ivermectin-sensitive Collies up to 20 times the dose
- Microfilariacidal action in dogs may result in circulatory collapse
- Safe to use in pregnant and lactating mammals.
- Dogs & Cats: 0.5 mg/kg, PO, once monthly
- Dogs: 0.5 mg/kg, PO, OD for Demodecosis

Macrocyclic Lactones / Macrolides Endoectocides

Moxidectin (Milbimicin B)

- Semi-synthetic derivative Nemadectin obtained from *Streptomyces cyanogrieus noncyanogenus*
- Endoectocide
- More lipophilic than other macrocyclic lactones
- Safe, non-toxic to ivermectin-sensitive Collies up to 20 times the dose
- Advised to remove microfilaria before M oxidectin treatment in dogs
- Dose
  - Cattle: 0.5 mg/kg, pour-on, 0.2 mg/kg, SC
  - Horse: 0.4 mg/kg, PO
  - Sheep: 0.2 mg/kg, PO
  - Dogs: 0.025 – 0.3 mg/kg, PO

Imidathiazoles

Tetramisole

- Two isomers – Levo & Dextro
- Levo form is active which is separated and marketed as Levamisole

Levamisole

- Available in two salt forms – phosphate and HCl,
- HCl salt is highly soluble in water – used as an injection
- It is also an immunomodulator – CMI – T cell differentiation
- MoA:
  - Autonomic ganglionic stimulant – stimulate both sympathetic and parasympathetic NS – muscular paralysis (nicotinic like action)
  - At high dose, interferes with carbohydrate metabolism by blocking fumarate reductase and succinate oxidase enzymes
- Anthelmintic spectrum: Anti-nematodal effect in cattle, sheep, swine, poultry
- No activity against tapeworm, cestodes and protozoa

Imidathiazoles

Levamisole

- PK:
  - Absorbed oral, skin and SC route, distributed widely, metabolised in liver and excreted in urine.
  - $T_{1/2}$ – cattle 4-6h, dog 1.8 -4 h, swine 3.5 – 7h. No residues in 7-8 days
- Narrower safety margin (TI: 5-6x), muscarinic and nicotinic cholinergic signs due to its mechanism of action.
- Signs of overdosage mimics OPC poisoning
- Antidote: Atropine sulphate, Hexamethonium (a ganglionic blocker)
- Drug Interactions:
  - Levamisole and OPC potentiate toxicity
  - Levamisole and chloramphenicol – death is reported
- Clinical Use: in cattle, sheep, goats, swine, poultry
- Dose:
  - cattle, sheep, goats, swine -8 mg/kg, PO - SD
  - Poultry – 25 – 50 mg/kg, PO

Tetrahydropyrimidines

Pyrantel

- Pyrantel salts (pamoate or tartrate) are photosensitive in solution form
- MoA: nicotine-like depolarising neuromuscular blocking agent
  - Slowly developing contracture and spastic paralysis of parasites
  - Inhibits acetylcholinesterase enzyme
  - Paralysed worms are slowly expelled (vermifuge)
- Active against all adult GI nematodes, less effective against larvae
- PK: Pyrantel pamoate is poorly soluble in water – no oral absorption, Pyrantel tartrate is water soluble – absorption occurs, with Tmax 2-3h
- Adverse effects:
  - Emesis in dogs and swine
  - Ataxia, tachycardia, profuse sweating – cholinergic effect
- Pyrantel pamoate is safe in puppies, pregnant and lactating animals
- Dose:
  - Dogs & Cats: 14.4 mg/kg as pamoate, PO – q3w
  - Horse: 6.6 mg(as base)/kg, PO
  - Swine: 22 mg/kg (as tartrate), PO
  - Cattle, Sheep & goats : 25 mg/kg(as tartrate), PO

Tetrahydropyrimidines

Morantel

- Methyl ester analogue of Pyrantel, available as tartrate salt
- MoA: similar to Pyrantel, also inhibits fumarate reductase in few nematodes
- Slower in onset of action but potent and safer than Pyrantel
- Active against all adult GI nematodes, less effective against larvae
- Used in ruminants and swine
- Dose:
  - Sheep: 10 mg/kg, PO
  - Cattle: 8.8 mg/kg, PO

Oxantel

- Narrow spectrum, effective against only whipworm
- Dose: Dogs – 55 mg/kg, PO

Organophosphorus Compounds (OPC)

- Narrow margin of safety
- MoA: inhibition of AChE

Dichlorvos

- Less active against ruminant nematodes, not safe in cattle and poultry
- Slow release formulation (incorporated in PVC resin pellets) – 48 hrs action
- Dose: Dogs, Horses, Pigs – 30 mg/kg, PO

Metrifonate (Trichlorfon)

- Prodrug of dichlorvos
- Dose: Horse -40 mg/kg, PO; Pigs – 50 mg/kg, 2 times

Organophosphorus Compounds (OPC)

Coumaphos

- Used as feed additive (as toxicity is observed at twice the therapeutic dose)
- Dose: Cattle & sheep – 2 mg/kg b.wt. in feed for 6 days

Haloxon

- Safety index 3-7 times the recommended dose, very toxic to foals
- Dose: Adult Horse -60 mg/kg, PO; Sheep & Pigs – 30-50 mg/kg, PO

Piperazines

- Safe in all species, active against ascarids

Piperazine

- Strong base, easily absorbs water and CO_2, protected from light and air in a tight container
- Available as various salts –citrate, adipate, phosphate, hexahydrate, chloride, sulphate and dihydrochloride
- Dosage of piperazine salt is expressed in terms of hydrate equivalent
  - 100 mg of Piperazine hydrate = 120 mg of piperazine adipate = 125 pip. Citrate
- MoA:
  - GABA agonist – Chloride channel – hyperpolarization – paralysis
  - Anticholinergic action at N-m junction
  - Blocks succinate production by worms
  - Worms paralysed, depletion of energy – lose their grip on intestinal wall – expelled alive in feces (vermifuge)
- Active against ascarids and nodular worms

Piperazines

Piperazine

- Rapidly absorbed orally, metabolized in liver, 30-40% excreted unchanged in urine
- Safe drug at recommended doses
- Should not be combined with pyrantel, because the MoA is antagonist
- Clinical use: treatment of ascarids in dogs, cats, swine and poultry
- Dose: expressed as hydrate
  - Dogs & Cats : 80 -100 mg/kg, PO
  - Ruminants : 110 mg/kg, PO
  - Horses: 250-300 mg/kg,PO
  - Poultry and Birds: 250 mg/kg, PO

Piperazines

Diethylcarbamazine

- MoA: similar to piperazine, inhibition of arachidonic acid metabolism in microfilarial org.- susceptible to host immune attack
- Active against filariasis and ascariasis in dogs and cats
- Drugs should be administered with food to avoid GI disturbances
- To prevent heart worm, should be administered one month before mosquito season, therapy continued until two months after end of season
- Used also to control *Dictyocaulus viviparous* infection – parasitic bronchitis
- Dose:
  - For prevention of heartworm infection
    - Dogs : 6.6 mg/kg, PO - OD
  - For treatment of ascarid and susceptible parasites
    - Dog : 55-110 mg/kg, PO
  - For treatment of Dictyocaulus infection
    - Cattle: 22 mg/kg, IM for 3 days or 44 mg/kg, IM - SD

Arsenicals

Thiacetarsamide

- MoA: Exact mechanism is not known, may be interaction between As with sulphydryl containing enzymes and proteins of the parasite
- Effective only against adult heartworms (*Dirofilaria immitis*)
- Administered by IV route only, concentrate in liver and kidneys
- Adverse effects: narrow margin of safety – vomiting, hepatotoxicity, nephrotoxicity and thrombocytopenia
  - Antidose: Dimercaprol (British Anti-lewisite)
- Dose: Dogs & Cats; 2.2 mg/kg, IV, BID – 2 days

Arsenicals

Melarsomine

- Effective only against adult heartworms (*Dirofilaria immitis*)
- Melarsomine is more efficacious, less irritating and less hepatotoxic
- Administered by deep IM, Tmax -3h, safety margin 2.5 – 3x of dose
- Adverse effects: overdosage – ataxia, stupor, cyanosis and death
- Contraindicated in cats due to severe toxicity
- Dose: Dogs ; 2.5 mg/kg, deep IM, twice at 24 h apart

Substituted Phenols and Sulphanilides

Commonly used as Anti-cestodal and Anti-trematodal drugs

Disophenol

- Effective against hookworms (Ancylostoma spp.) in dogs and cats, gapeworm (*Syngamus trachea*) in turkeys
- Given by either oral or parenteral route, well absorbed by oral route
- Adverse effects: overdosage – tachycarida, polypnea, hyperthermia and lenticular opacity
- Dose: Dogs ; 10 mg/kg, SC, repeated after 3 weeks

Octadepsipeptides

Emodepside is the only drug – for use in cats

Emodepside

- Act by binding to GPCR called latrophilins – Ach release & inhibitory neurotransmitter release – opens chloride channel – hyperpolarisation - muscle paralysis in nematodes

(http://www.animalhealth.bayer.com/5435.0.html)

- Available in combination with Praziquantel (1.98% emodepside + 7.94% praziquantel) – topical application
- Absorbed through hair follicles – enters systemic circulation – kills roundworms and hook worms.
- Praziquantel is converted in to active form in liver and kills tapeworms
- Dose: Cats: 3 mg/kg (emodepside) + 12 mg/kg (praziquantel) – spot on re-apply if required after 30 days

Aminoacetonitrile Derivatives

Monepantel is the only drug – for use in sheep

Monepantel

- Act by binding to a specific receptor 'Hco-MPTL-1' found only in nematodes – paralysis and subsequent death of parasites
- Safety margin is 10x
- Irritant – direct exposure to skin should be avoided
- Administered by drench to control GI nematodes in sheep
- Dose: sheep: 2.5 mg/kg,PO

Miscellaneous Antinematodal Drugs

Phenothiazine

- Old Anthelmintic (1930s)
- MoA: inhibit enzymes involved in parasite's carbohydrate metabolism
- Effective against adult nematodes, ineffective against larval and immature
- PK: Oral F~50%, unabsorbed – antinematodal effect
- Phenothiazine is converted to phenothiazine sulphoxide in intestinal epithelium – converted in to brown colored dyes – phenothiazone and thionol in liver – stains brown red to urine, milk for several days
- Narrow margin of safety – hemolysis, photosensitization
- Dose:
  - Cattle: 20-60 g (total), PO
  - Sheep: 5 -20 g(total), PO
  - Horses: 10 -30 g (total), PO

Miscellaneous Antinematodal Drugs

Tetrachlorethylene

- High efficacy against hookworms and some trematodes in dogs and cats
- It is not useful in ruminants, rapidly inactivated in rumen
- Overnight fasting is required in small animals, as absorption increases toxicity
- Rarely used
- Dose: Dogs & Cats – 0.22 ml/kg, PO in gelatine capsule

Toluene

- Derived from coal tar
- Effective against Ascarids and hookworms in dogs and cats
- MoA: either irritant or depressant effects on the neural cells of parasites
- Fasting is required
- Dose: Dogs & cats -0.22 ml/kg, PO

Miscellaneous Antinematodal Drugs

Thenium closylate

- Dose: Dogs (<5kg): 125 mg(total), PO, SD

Phthalofyne

- Used against whipworms in dogs
- Dogs: 200 mg/kg, PO; 250 mg/kg, IV

Dithiazanine Iodide

- Broad spectrum anthelmintic activity
- Dogs: 20 mg/kg, PO – OD for 2-7 days

Hygromycin B

- Antibiotic from *Streptomyces hygroscopicus*.
- Effective against GI round worms and is used in pigs and poultry.
- Replaced by drugs with higher efficacy, broader spectrum and lower toxicity

Anti-Cestodal Drugs

- Taeniafuge – expels tapeworms
- Taeniacides (cestocides) – kills tapeworms *in situ*
- Classification

I. Synthetic Anticestodal drugs
   1. Isoquinolones – Praziquantel and Epsiprantel
   2. Salicylanilides – Niclosamide
   3. Substituted Phenols – Dichlorophen, Nitroscanate, Bithionol
   4. Benzimidazoles and Probenzimidazoles – Albendazole, etc.
   5. Miscellaneous agents – Bunamidine, Resorantel, Uredophos

II. Natural Anticestodal drugs
   1. Organic compounds – Rhizome of male fern, Kamala, Arecoline
   2. Inorganic compounds – Tin oxide, Tin chloride, Lead arsenate

Isoquinolones

Praziquantel

- Broad spectrum – Anticestodal and Antitrematodal
- MoA
  - Increased permeability to Ca^{++} leads to spastic contraction & paralysis
  - Protective integument of parasite is destroyed
  - Lose the grip – susceptible to proteolytic digestive enzymes of the host
- PK:
  - Completely absorbed, undergo first pass metabolism
  - Widely distributed to brain, CSF, muscles, intestines, peritoneal cavity, bile ducts
  - Metabolised by CYP3A4 – inactive metabolites
  - Excreted in urine, t1/2 – 3h dogs
- No teratogenic or embryotoxic effects, mild GI disturbances
- Dose:
  - Dogs & Cats: 5 mg/kg, PO
  - Birds, Sheep & Goats: 10-15 mg/kg, PO
  - Horses : 0.5 – 1.5 mg/kg, PO

Isoquinolones

Epsiprantel

- Poorly absorbed orally
- Wide margin of safety, dose as high as 100 mg/kg – well tolerated by dogs and cats
- Can be given in combination with Diethycarbamazine
- Dose:
  - Dogs : 5 mg/kg, PO, SD
  - Cats: 2.5 mg/kg, PO, SD

Salicylanilides

Niclosamide

- Broad Spectrum: *Diphylidium, Taenia, Echinococcus, Moneizia*, intestinal flukes, *Paramphistomum*
- MoA
  - Inhibit oxidative phosphorylation and glucose absorption - taenicide
- PK: Poorly absorbed, taenicidal action in the intestine
- Given after 12 hours of fasting, combined with saline purgative to remove all dead tapeworms
- Replaced in veterinary medicine by modern cestocides
- Dose:
  - Dogs & Cats: 100 - 150 mg/kg, PO
  - Cattle: 50 mg/kg, PO
  - Sheep & Goats: 100 mg/kg, PO
  - Birds : 220 mg/kg, q10-14d
  - Rabbits: 150 mg/kg, PO, q10-14d

Substituted Phenols

Dichlorophen

- Narrow Spectrum: *Diphylidium & Taenia*
- MoA:inhibit oxidative phosphorylation –leads to depletion of energy
- PK: Poorly absorbed, taenicidal action in the intestine
- Replaced in veterinary medicine by modern cestocides
- Dose: Dogs & Cats: 200 mg/kg, PO

Nitroscanate

- Used only canines, safety margin – 40x
- Dose- Dogs: 50 mg/kg, PO

Bithionol

- Antibacterial, antifungal and anthelmintic

Benzimidazoles and Pro-Benzimidazoles

- Albendazole, Fenbendazole, Mebendazole, etc.
- Pro-drugs – Febantel, Netobimin
- Effective against mature Taenia and Echinococcus in dogs and cats
- Moniezia in ruminants
- Kill intermediate cysts of Taenia in sheep and cattle
- Not effective against Diphylidium tapeworms

Miscellaneous Drugs

Bunamidine

- Effective against tapeworms of dogs
- MoA: decreasing glucose uptake by worms – taenicide
- Less used in veterinary practice due to its cardiac toxicity
- Dose: Dogs & Cats: 25 -50 mg/kg, PO – SD on an empty stomach

Resorantel

- Anthelmintic used in sheep and other ruminants
- Act by interfering glucose metabolism in parasites
- Safe in pregnant animals
- Dose- Sheep: 65 mg/kg, PO, given 2-3 days before lambing

Uredophos

- Broad-spectrum anthelmintic, not used nowadays due to adverse effects

Natural Anticestodal Drugs

Natural Organic Compounds – taenifuge, often combined with purgatives or laxatives

Male Fern (Aspidium)

- Active constituents – filmrone, filicic acid and flavaspidic acid (most potent)
- Transient paralysis of GI tapeworms
- Saline purgative should be given 12 hours prior to administration of fern.
- Oleoresin present in male fern – cause liver damage
- Dose: Dogs -1.4 ml, Sheep – 4 ml, Cattle & Horses – 15-45 ml (liquid extract) – PO

Kamala (Rottlera)

- Obtained from hair and glands covering the fruit of plant Mallotus Philippinensis
- Active ingredients – rottlerin and isorottlerin – taenifuge action in dogs, cats, poultry
- It causes initial stimulations followed by paralysis of tapeworm
- Increases the peristaltic movement of host gut by producing irritation of GI tract
- Dose: Dogs- uo to 8 g, Cats – 0.6 -1 g and Poultry – 0.5 -2 g, PO

Natural Anticestodal Drugs

Natural Organic Compounds – taenifuge, often combined with purgatives or laxatives

Arecoline

- Obtained from dried ripe seeds of Areca catechu – Betelnut
- Arecoline salt (HBr) is stable
- Arecoline is cholinomimetic
- Causes transient paralysis – require purgation, else the worms regain its activity
- HBr salt is Not recommended in cats – due to excessive secretions and brochoconstrictions
- Dose: Arecoline HBr – 1 mg/kg, PO; Arecoline acetarsal – Dogs & Cats – 5 mg/kg,PO

Natural Anticestodal Drugs

Inorganic Compounds

- Tin oxide, Tin chloride and Lead arsenate – low safety margin – not used nowadays

Antitrematodal Drugs

Classification

- Substituted Phenols – Nitroxinil, Hexachlorophene, Niclofan and Bithionol
- Salicylanilides – Closantel, Rafoxanide, Oxyclozanide, Brotianide, etc.
- Aromatic amides – Diamfenetide
- Sulphonamides – Clorsulon
- Halogenated hydrocarbons – CCl4, Hexachloroethane, etc.
- Benzimidazoles and Pro-benzimidazoles - Albendazole, triclabendazole, etc.
- Isoquinolones – Praziquantel
- Miscellaneous drugs – Niridazole and Stibophen

Substituted Phenols

Nitroxinil

- Injectable fasciolicide, active against Haemonchus
- MoA: uncoupling of oxidative phosphorylation – depletion of ATP
  - Similar effect is also observed in mammalian mitochondria – less safety margin
- PK:
  - oral admin. in ruminants – metabolised and destroyed by rumen microbes,
  - SC inj. – Tmax 30-60min,
  - high PPB, detectable level in plasma and liver up to 2 months in sheep
- Adverse effects: 4x safety margin, GI disturbances,
  - High dose – blindness and classical signs of uncoupling phosphorylation – hyperthermia, hyperventilation, convulsions, tachycardia, death
  - Stains wool in sheep
- Dose:
  - Cattle & Sheep : 10 mg/kg, SC
  - Game birds : 24 mg/kg, PO in drinking water

Substituted Phenols

Niclofolan

- Active against immature and mature form of fasciola, active in oral and SC
- Dose: Cattle, Sheep & Pigs: 3 -5 mg/kg, PO

Bithionol

- Active against rumen and liver flukes
- Combined with Hexachlorophene for high efficacy
- Toxicity due to uncoupling of phosphorylation
- Dose: Cattle & Sheep: 60 mg/kg, PO as a bolus or in feed

Salicylanilides

MoA: uncoupling of oxidative phosphorylation

Closantel

- Broad-spectrum, active against juvenile and adult fasciola, nematodes and some tapeworms
- Also active against mange mites, ticks and parasitic larvae of flies
- No effect on Paramphistomum flukes
- PK: Oral – well absorbed, Tmax – 24 h, PPB >99%, excreted in feces (80%), t1/2 – 15 days in sheep
- Adverse effects: Safety margin 6x, toxicity characteristic of oxidative phosphorylation inhibition, embryotoxic
- Used to treat ivermectin, benzimidazole, levamisole/morantel and rafoxinide resistant strains of the parasite
- Dose: Cattle & Sheep : 5 mg/kg, SC or 10 mg/kg, PO

Salicylanilides

Rafoxinide

- Broad-spectrum, active against juvenile and adult fasciola, nematodes and sheep nasal bot (*Oestrus ovis*)
- PK: Oral – well absorpbed, Tmax – 24-48 h, PPB >99%, excreted in feces (80%), t1/2 – 16 days in sheep
- Safety margin 6x
- Dose: Cattle & Sheep : 3 mg/kg, SC or 7.5 mg/kg, PO

Oxyclozanide:

- 4x safety margin in sheep, withdrawal time - 14 days
- Combined with levamisole – broad spectrum
- Dose: Cattle & sheep – 10-15 mg/kg, PO

Aromatic Amines

Diamfenetide

- Active against only immature form of flukes
- MoA: not known, vacuolation of flukes integument, induce paralysis
  - Metabolised in liver to active drug, acts on immature flukes, get destroyed in liver
- PK: Oral – well absorbed, deacylated in liver, conc. increases in liver and bile after 3 days of dosing, excreted in milk
- Adverse effects: Safe at recommended dose, high dose – impairment of vision and wool loss
- Used in combination rafoxinide – prophylaxis against fasciola
- Dose: Sheep : 100 mg/kg, PO

Sulphonamides

Clorsulon

- MoA: inhibit enzymes in Embden-Meyerhof glycolytic pathway – deprive energy source in flukes
- PK: Oral – well absorbed, highly lipophilic, Tmax – 4h, PPB~75% and RBC binding~25%
- Adverse effects: Safety index 25x, excreted in milk - cow
- Used in combination with ivermectin – against fasciola and nematode, withholding period is 8 days for slaughter
- Dose: Cattle & Sheep : 7 mg/kg, PO or 4 mg/kg, SC or
  2 mg/kg Clorsulon + 0.2 mg/kg ivermectin, SC

Halogenated Hydrocarbons

Carbon tetrachloride

- First drug introduced for the treatment of fascioliosis
- MoA: formation of toxic metabolite, inhibit cholesterol synthesis and accumulation toxic methyl sterols in the target parasites – probable MoA
- PK: Oral – slowly absorbed, metabolites – released in bile, elimination is by – expired air (volatile) via lungs
- Adverse effects: narrow safety margin, CNS depression, renal damage, circulatory collapse, death
- Not commonly used in vet practice, if used should be given with liq.paraffin
- Dose: Sheep : up to 4ml PO

Benzimidazoles

Albendazole, Fenbendazole, Netobimin – Broad spectrum -Already discussed

Triclabendazole

- Flukicide in cattle, sheep, goats and horses
- No activity against nematodes and cestodes
- Well absorbed orally, metabolised to sulphoxide and sulphone, high PPB
- Withdrawal period 28 days- should not be given to lactating animals
- Combined with ivermectin to treat fasciola, roundworm and ectoparasites
  - Triclabendazole -36% + Ivermectin – 0.6% -S/C
- Dose: Sheep & Goats – 10 mg/kg, PO; Cattle & horses – 12 mg/kg,PO

Luxabendazole – broad spectrum; sheep – 10 mg/kg, PO

Isoquinolones

Praziquantel – Anticestodal and effective against flukes - Already discussed

Miscellaneous Drugs

Niridazole

- Active against Schistosoma.
- MoA: concentrate in parasite and inhibits oogenesis and spermatogenesis, inhibit phosphofructokinase – glycogen depletion in flukes – lose their hold in mesenteric veins – undergoes hepatic shift –die and phagocytosed
- Not used commonly due to adverse effects – CNS toxicity (hallucinations) in human
- Allergic to sensitive individual
- Niridazole is used as Schistosomicide, other anthelmintic do not produce desirable effect

Stibophen

- Crystalline antimony derivative, effective against Schistosoma
- MoA – same Niridazole
- Intramuscular injection