

Drugs for the treatment of hookworm

Bephenium, a nicotine-like quaternary ammonium compound, is used mainly in dogs and cats to treat hookworm (*Ancylostoma caninum* or *Uncinaria stenocephala*) infection. It is effective to a lesser extent against *Toxocara* and *Trichuris*. In ruminants, bephenium has specific action in *Nematodirus* infestations (which are not of importance in Nigeria).

Bephenium is poorly absorbed by the host and has low toxicity, causing only vomiting in some (about 19 percent) of the dog treated. **Thenium closylate**, an analogue of bephenium is used strictly in dogs to control hookworms. It is 98 percent effective against adult and immature stages of *A. caninum* and *U. stenocephala*. It is moderately effective against ascarids. The combination is used in weaned puppies and dogs infested with both hookworms and roundworms. Thenium and bephenium are administered orally in from the gut because of their quaternary structure.

Dose

Bephenium, oral dosage:

Cattle	200mg/kg
Small ruminants	200mg/kg
Dogs and cats	30mg/kg, repeat after 6-10 hours.

Thenium, oral dosage to be given in two parts: one dose before feed and second 3 hours after the feed:

Dogs	55mg/kg
Puppies	25-27 mg/kg

Adverse effects. Thenium closylate has a wide margin of safety because absorption from the gut is limited. Vomiting may occur in 20 percent of treated dogs. Rarely, sudden death may occur following dosing with thenium.

Drugs for heartworm prevention and therapy

Treatment and prevention of heartworm involve three aspects: removal of adult worms (requires an **adulticide**, which eliminates both immature, L₅, and adult heartworm); interruption of the life cycle (requires a **microfilaricide**, which should be initiated 3-4 weeks after adulticide treatment), and prevention (requires a **larvicide**).

Adulticides

Thiacetarsamide, a trivalent arsenic compound, is the only commercially available adulticide. It denatures enzymes by binding to the sulphhydryl groups of cysteine residues. Following intravenous injection, the drug is widely distributed, but concentrated in the liver and kidneys. It is metabolized in the liver with an elimination half-life of 45 minutes. About 85 percent of the dose is eliminated within 48 hours, primarily in the faeces, and some in the urine. Following four intravenous injections of the disodium salt (2.2 mg/kg, twice daily for 2 days), adult worms gradually die, usually within 5-14 days. There is no effect on circulating microfilariae. Dead or dying adult worms swept out of the heart by the blood flow, lodge in the branches of the pulmonary artery. Here phagocytosis of the dead worm occurs during the next 2-3 months.

Adverse effects: Thiacetarsamide has a narrow margin of safety. In case of overdose, dimercaprol (BAL) can be used as an antidote. Tissue sloughing and phlebitis may occur if the drug is into perivascular space. Dogs may vomit after thiacetarsamide administration, which is both hepatotoxic and nephrotoxic. Thromboembolic pneumonia may result as dead heartworms accumulate, usually in the caudal lung lobes.

Melarsomine is also a trivalent arsenic compound; its advantages over thiacetarsamide are that melarsomine can be administered intramuscularly, and is retained in the body five times longer than thiacetarsamide. Melarsomine is found in both plasma and red blood cells, whereas thiacetarsamide is found only in red blood cells. The usual dose of melarsomine is 2.5 mg/kg, once daily for 2 days. The first dose should be injected in the right lumbar muscles and the second in the left. For dogs with severe infection, a single dose (2.5 mg/kg) is followed by the full two-dose treatment 1 month later.

Adverse effects. Localized oedema and hindlimb weakness may occur following intramuscular injection. Hepatotoxicity, renal toxicity and thromboembolic pneumonia may occur. Overdose may result in distress, restlessness, tachycardia, dyspnoea, pawing, vomiting, and recumbency. Toxicity can be reversed by intramuscular injection of 3 mg/kg *dimercaprol* (BAL) within 3 hours of the onset of symptoms.

Microfilaricides

Ivermectin and **milbemycin** are the only two drugs that may be safely and effectively used as extralabel microfilaricides. They are larvicidal and kill the L larvae. As a microfilaricide, *ivermectin* therapy entails one dose (50 µg/kg), administered orally or subcutaneously. It may

cause toxicity in certain blood-lines, for example, rough-haired collies, and is contraindicated in this breed. One dose of *milbemycin* (0.5 mg/kg) is administered orally; the dose may be repeated in 2 weeks. The drug can be safely used in collies. When used as larvicide, **ivermectin** is administered orally at dosage of 6-12 μ g/kg once monthly.

Dithiazanime iodide is a cyanine dye derivative used as a microfilaricide in dogs. It may clear circulating by making the microfilariae to lose motility, become trapped. It may clear circulating by making the microfilariae to lose motility, become trapped in capillary beds, and are eventually phagocytised by host cells. Studies with canine whipworms indicate that the drug cause an irreversible inhibition of glucose absorption, resulting in a marked reduction in free glucose and a consequent depletion in energy-rich phosphate bonds. Dithazanine iodide is given at a dose rate of 6.6-11 mg/kg as a filaricide. It is one of a few drugs that can be used successfully against *Strongyloides stercoralis* infections in dogs. A daily dose of 22 mg/kg for 12days is recommended. At this dose, vomiting and diarrhea are very likely to occur. The daily dose should therefore be split, giving it twice a day during meals.

Larvicides

Diethylcarbamazine is a synthetic methylpiperazine derivatine. Its chief value is as a prophylactic treatment of heartworm (*Dirofilaria immitis* infection. It kills the L₃ larvae, thereby eliminating stages L₃ - L₅ of the heartworm life cycle. It also has an effect on the muscular activity of the microfilariae and adult worm so that they are dislodged and killed more slowly. It reduces the worm burden in ascariasis and strongyloidosis of small animals, but efficacy is low. After an oral dose, plasma levels peak at 3 hours and fall to zero in 48 hours. The therapeutic level of diethylcarbamazine has to be maintained by daily dosing. About 10-30 percent of the dose is excreted as an unchanged drug in urine; the rest is excreted as metabolites.

Dose:

For heartworm prophylaxis, diethylcarbamazine citrate (6-11 mg/kg daily, per os) is administered during and 2 months after the mosquito season.

For *ascariasis* and *strongyloidosis* in small animals, the dose is 30-35 mg/kg, administered orally after feeding or with food.

Adverse effects: Reaction to diethylcarbamazine itself is mild and transient if there are no microfilariae in the blood stream. Unwanted effects start within 2-4 hours: malaise, anorexia, and weakness are frequent; nausea, vomiting, dizziness and sleepiness occur less often. The drug

may cause potentially fatal anaphylactic reaction in microfilariae-positive dogs. The reactions result from the release of foreign proteins from dying microfilariae or adult worm that may constrict the hepatic vein.

Drugs for the treatment of cestodes

Cestodes (or true tapeworms) typically have a flat, segmented body and attach to the host's intestine. Tapeworm infection (*taeniasis*) is a disease of young animals. In ruminants, treatment is rarely indicated after they reach 6 months of age; lambs less than 2 months should not be treated. Although adult tapeworm do not usually cause discernible disease, treatment is often necessary for public health reasons; to prevent disease due to larval stages in farm animals; to minimize meat inspection losses, and for aesthetic reasons in dogs and cats. All tapeworms have an indirect life cycle and preventive measure often include control of intermediate hosts (e.g. fleas for *Dipylidium*, and rodent for *taenia*). Anticestodal agents kill tapeworms as opposed to **arecoline**, an obsolete taeniafuga that only paralyzes them. But an arecoline purge (5-15mg) is still sometimes used as the only effective means of diagnosing *Echinococcus granulosus* infection in dogs, since the eggs are indistinguishable from those of *Taenia* species and the adult tapeworm must be identified. Worms killed by taenicides may be digested by the host animal; therefore, they may not be evident in the faeces.

Praziquantel

Praziquantel and its analogue **episiprantel** are synthetic isoquinoline-pyrazine derivatives. Both drugs have high efficacy against cestodes and are effective in the treatment of schistosome infections of all species and most other trematodes. However, their activity against *Fasciola hepatica* or hydatid cyst in humans is erratic.

Pharmacokinetics-

In dogs, praziquantel is readily absorbed orally. Peak plasma levels occur in one-half to one hour. About 80 percent of the drug is bound to plasma proteins. It undergoes extensive first-pass metabolism in the liver to many inactive products, which limits its bioavailability. Praziquantel is distributed throughout the body, including the CNS, where it attains therapeutic concentrations, making it useful in human neurocysticercosis. It is excreted primarily in the urine. The elimination half-life is 3 hours in dogs.

Dose

Dog, Cat 5mg/kg PO; 3.5-7.5 mg/kg SC or IM

Horse 10 mg/kg PO

Epsiprantel at 5 mg/kg per os is highly effective against adult *E. granulosus*, but 10mg/kgm are required for high activity against 7-days-old *E. granulosus*.

Adverse effects: Praziquantel has a good safely margin; its adverse effects are mild and transient. They include dizziness, drowsiness and lassitude.

Bunamidine

Bunamidine is effective against the common tapeworm species. It is most effective if given after fasting. A single treatment is effective against *Taenia* and *Dipylidium* species, but a second dose should be given in *Echinococcus* infestations after an interval of 6 weeks (the prepatent period for this parasite is about 47 days). Bunamidine is active against *Moniezia expansa* and *M. benedeni* in sheep and goats. It is absorbed orally and metabolism in the liver. It causes digestion of the tapeworm in the gut of the host.

Dose

Dogs, cats' 20-40 mg/kg PO

Sheep, goats' 25-50 mg/kg PO

Adverse effects: Vomiting and mild diarrhea may be seen; exercise or excitement should be avoided in dogs soon after administration of the drug.

Niclosamide

Niclosamide is a salicylanilide derivative. It was the drug of choice for tapeworm infection but has now largely been superseded by *praziquantel*. *Niclosamide* is active against most types of tapeworm including *Anoplocephala* of horses, *Moniezia* and *thysanosoma* of sheep, *Taenie* and *dipylidium* species of dogs and cats. it is only 50 percent effective against *Echinococcus* and the manufacturers recommended using four times the normal dose in such infections (*praziquantel* would be more appropriate), it has activity against intestinal flukes such as *paramphistomum* in ruminants.

Pharmacokinetics. Niclosamide is administered orally in tablet form to dogs and cats, and as a drench to ruminants. The animals should be fasted overnight before treatment. There is negligible absorption from the gastrointestinal tract; the bulk of the dose remains in the lumen of the gut where it exerts its taenicidal effect. The small amount that is absorbed is metabolized to the relatively inter amine, aminoclosamide.

Dose, per os

Dogs, cats	125 mg/kg
Cattle	50mg/kg
Sheep, goat	77 mg/kg

Adverse effects: Niclosamide has a good safety margin; it can be used in pregnant and young animals. Unwanted effects are mild – nausea and vomiting can occur.

Drugs for the treatment of trematodes

The trematodes (flukes) are leaf –shape flatworm that are generally characterized by the tissues they infect (liver, lung, intestinal, or blood flukes). The liver flukes (*fasciola hepatica*) is endemic in many wet region and affects mainly ruminants kept in or emanating from such areas. The intermediate host is a mud snail, *Lymnea truncatudes*. Some benzimidazoles (**albendazole, netobimin, triclabendazole**); salicylanilides (**brotianide, clioxanide, closantel, niclosamide, oxyclozanide, rafoxanide**); substituted phenols (**bithionol, disophenol, hexachlorophene, niclofolan, nitroxynil**); the aromatic amide **diamphenethide**, and the sulphonamide **clorsulon** are effective flukicides, but none has a wide therapeutic index.

Pharmacokinetics. Pharmacokinetic data for many modern fasciolicides is sparse. Peak plasma levels are reached in 12-24 hours for salicylanilides and 3-4 days for bithionol. The absorption of fasciolicides given parenterally (e.g. nitroxynil) is rapid and complete plasma levels peak 30-60 minutes after dosing. Nitroxynil is destroyed by rumen microorganisms if administered orally to ruminants; this restrict its administered to subcutaneous injection. The relatively high residues of nitroxynil found in milk are due to the relatively high dose parental administration, and the tendency to form stable complexes with plasma and tissue proteins. After absorption, diamphenethide is metabolized in the liver to an amine metabolite that is active against flukes. Little of the metabolite reaches the bile duct, so that activity against adult flukes is poor. *Oxyclozanide* is metabolized in the liver to the active glucuronide, which is secreted in the bile in high concentrations in the vicinity of the adult fluke.

Clinical uses. The benzimidazole flukicides (albendazole, netobimin) are active against mature *F hepatica* and *Dicrocoelium dendriticum*. *Triclabendazole* is highly effective against all liver stages of *Fasciola*. In vivo, salicylanilides (e.g. *niclosamide*), substituted phenols (e.g. *bithionol*)

affect mainly the adult flukes, with variable activity against the immature flukes in liver parenchyma.

Dose

Closantel

Cattle, Sheep 10mg/kg PO, or 5mg/kgSC

Nitroxynil

Cattle, Sheep 10mg/kg SC

Oxyclozanide

Cattle, Sheep 10-15 mg/kg PO

Rafoxanide

Cattle, Sheep 7.5 mg/kg PO or 3.5 mg/kg SC

Diamphenethide

Sheep 100 mg/kg PO

Clorsulon

Cattle, Sheep 7 mg/kg PO or 4 mg/kg SC

Niclofolan

Cattle, Sheep 3 mg/kg PO

Vaccination against certain helminthes

Active immunization can be induced to lungworm and hookworm infection. A special type of live vaccine (**irradiated third stage larvae of *dictyocaulus viviparous***) is available for protecting calves against infection by the lungworm. This vaccine consists of two does of 100 irradiated third stage at an interval of one month. A similar vaccine (irradiated infective larvae of *Ancylostoma canium* and *Uncinaria stenocephala*) has also been devised to protect puppies and dogs against hookworm.

ANTINEOPLASTIC DRUGS

Antineoplastic drugs are administered to animals in an attempt to cure or lessen the effect of neoplasm.

Principles of chemotherapy

The proliferating cells, whether they are found in normal tissue or in neoplasms, contain resting and dividing cells that are involved in phases of cell cycle.

The phases of cell cycle include:

S-phase (D.N.A synthesis)

M-phase (mitosis)

G₁-phase of R.N.A synthesis

G₂-phase of R.N.A synthesis

G₀ (resting phase)

Chemotherapy is most effective against rapidly growing tumors because actively dividing cells are more sensitive to D.N.A damages and cell cycle processes.

Factors affecting chemotherapy

The length of time that a tumor is exposed to an effective dose of drug.

The development of specific resistance to a drug by the tumor

MTD (maximum tolerated dose)

Metronomic method (Low dose over a relative long period)

Tendency of toxicity is possible so constant monitoring of patient is very important this could interfere with the effectiveness of the drug

The combinations effective to the particular situation, if there is resistance.

Proper diagnostic tool used to diagnose the phase of tumor for appropriate and rational use of drugs.

Patient status.

Immunologic, health, pregnant or not, Age, breed, specie.

The main anticancer drugs can be divided into the following general categories

Cytotoxic agents includes alkylating agents (nitrogen mustards and alkylsulfonates); anti metabolites (folate, purines and pyrimidine antagonist); Microtubule inhibitors (Vinc alkaloids, taxanes, epipodophyllotoxins, vinorelbine), and cytotoxic antibiotics.

Enzymes; interferons; monoclonal antibodies.

Steroid hormones and their antibiotics

Miscellaneous agents that do not fit the above categories (e.g. hydroxyl urea, procarbazine, mitotane, cisplatin, carboplatin) . protein fragments (angiostatin and endostatin used in therapy of mice tumors. They interfere with blood supply to tumor cell this leads to reduction in size of tumor regression.

Alkylating Agents

Examples:- nitrogen mustard, cyclophosphamide, ifosfamide, mechlorothamine, thiotepa

Mechanism of action

- Alkylating agents act by transferring alkyl group to D.N.A in N-7 position of guanine in cell division.
- Lead to breakage of D.N.A
- These agents are not cell-cycle specific.

Dog, cat

50mg/m² BSA p.o every secondly
100mg/m² BSA IV every 3weeks.

Therapeutic uses:-

Cyclophosphamide is widely used alone or in the combination in the treatment of

- Lymphoproliferative diseases
- Transmissible venereal tumor
- Bladder carcinomas

Adverse effect: Nausea, vomiting, diarrhea, myelosuppression, alopecia, and haemorrhagic cystitis (caused by acrolein, which can irritate the bladder).

Thiotepa: can be administered intravenously, but is usually administered by intrathoracic injection for pleural resulting from thoracic metastases.

Therapeutic use :- bladder tumor (e.g. transitional cell carcinoma). It is used in mastocytomas, the drug has high toxicity and not used frequently in veterinary.

Melphalan: Is very effective in multiple myeloma of dogs and cats. It has been suggested for the treatment of lymphoreticular neoplasms, osteosarcomas, mammary gland and lung tumors. Bone marrow depression is the major toxic effect of melphalan.

Pharmacokinetics

- Cyclophosphamide is the most commonly used alkylating in veterinary medicine
- When orally absorbed
- Widely distributed to all tissues except the C.N.S.
- It is hydroxylated in the liver as the first step in its conversion from inactive to metabolites.

- Phosphoramidate mustard and acrolein.
- Its metabolites are excreted by the kidneys within 48 -72hours.

Antimetabolites

Antimetabolites are structurally similar to folic acid, pyrimidines, or purines. They interfere with the availability of normal nucleotide precursors by inhibiting their synthesis or by competing with them in D.N.A or R.N.A synthesis they “deceive” or “defraud” bodily process: they are most effective during ‘S’ Phase.

Folate antagonist

Methotrexate is a folic acid analogue. It inhibits dihydrofolate reductase, an enzyme that converts folic acid to its active coenzyme form, tetrahydrofolic acid. (Folinic acid) is essential cofactor in the synthesis of D.N.A, R.N.A and protein. Methotrexate has an un usually (50,000times) higher affinity for dihydrofolate reductase than the normal substrate, dihydrofolate. This drug is reversed by leucovorin, administration of this drug is “folinic acid rescue”

Pharmacokinetics

- Methotrexate is readily absorbed orally
- It is distributed to all tissues except the C.N.S
- Largely excreted unchanged in urine.
- Aspirin and sulphonamides decreases its renal tubular secretion and enhances its toxicity.

Therapeutic uses

Methotrexate, often used in combination with cyclophosphamide and vincristine.

- Is effective against transmissible venereal tumor in dogs.
- Choriocarcinoma.
- Acute lymphatic leukaemia
- Used in treatment of rheumatoid arthritis with a prostaglandin.

Adverse effects:

- Nausea
- Vomiting
- Diarrhea

- Megaloblastic anaemia
- Deformation of intestinal epithelium and beading may occur.
- Some of these are reversed by leucovorin.