

VPC 402 LECTURE NOTE

TOPIC : ANTHELMINTICS

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Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminthes. Helminthiasis is prevalent globally (1/3 of world's population harbours them), but is more common in developing countries with poorer personal and environmental hygiene. Multiple infestations in the same individual are not infrequent. In the human body, g.i.t., is the abode of many helminthes, but some also live in tissues, or their larvae migrate into tissues. They harm the host by depriving him of food, causing blood loss, injury to organs, intestinal or lymphatic obstruction and by secreting toxins. Helminthiasis is rarely fatal, but is a major cause of ill health.

Many drugs were discovered in the early part of the present century. However, over the past 3 decades many new, highly efficacious and well tolerated. Anthelmintics have been developed. These have largely replaced the older drugs. Drugs like pyrvinium and gentian violet (for thread worm), tetrachloroethylene, bephenium and bitoscanate (for hook worm), dichlorophen and paromomycin (for tape worm) are no longer used. The choice of drug for each worm infestation is based not only on efficacy, but also on lack of side effects/toxicity, ease of administration (preferably) single dose) and low cost.

Development of resistance had not been a problem in the clinical use of anthelminitics. The current choice of drugs for worm infestations common in Indian subcontinent is given in Table 1.

Mebendazole

It is a benzimidazole introduced in 1972. this congener of thiabendazole became very popular because it retained the broad spectrum anthelmintic activity but not the toxicity of its predecessor. It has produce nearly 100% cure rate/reduction in egg count in round worm, hook worm (both species), Enterobius and Trichuris infestations, but is much less active on Strongyloides. Upto 75% cure has been reported in tape worms, but H. nana is relatively insensitive. It expels Trichinella spiralis from intestines, but efficacy in killing larvae that have migrated to muscles is uncertain. Prolonged treatment has been shown to cause regression hydatid cysts in the liver. Treatment after resection of the cyst may prevent its regrowth.

The immobilizing and lethal action of mebendazole on worms is rather slow; takes 2-3 days to develop. It acts probably by blocking glucose uptake in the parasite and depletion of its glycogen stores. Intracellular microtubules in the cells of the worm are gradually lost. The site of action mebendazole appears to be the microtubular protein β -tubulin' of the parasite. It binds of β -tubulin of susceptible worms with high affinity and inhibits its polymerization. Hatching of the parasite eggs and their larvae are also inhibited, ascaris ova are killed.

Pharmacokinetics: Absorption of mebendazole from intestines is minimal; 75-90% of an oral dose is passed in the faeces. The fraction absorbed is excreted mainly as metabolites in urine.

Adverse effects mebendazole is well tolerated even by patients in poor health. Diarrhea, nausea and abdominal pain have attended its use in heavy infestation. Incidents of expulsion of Ascaris from mouth or nose have occurred, probably due to starvation of the parasite and their slow death. Allergic reactions loss of hair and granulocytopenia have been reported with high doses.

Safety of mebendazole during pregnancy is not known, but it is contraindicated on the basis of animal data.

Uses and administration mebendazole is available as: MEBEX, MENDAZOLE, WORMIN 100 mg chewable tab and 100 mg/5ml suspension. The dose and duration of treatment is the same for children above 2 years as for adults, ½ dose for 1-2 yr age.

Round worm	100mg twice a day for 3 consecutive days.
Hook worm	no fasting, purging or any other preparation of
Trichuris	the patients in needed.

Enterobius: 100mg single dose, repeated after 2-3 weeks (to kill the ova that have developed later). Strict hygienic measures and simultaneous treatment of all children in the family or class is advocated to cut down autoinfection and person infection. This holds true of enterobiasis, irrespective of drug used.

Tape worms: 200 mg BD for 4 consecutive days (less effective).

Trichinella spiralis: 200 mg BD for 4 days; less effective than albendazole

Hydatid disease: 200-400 mg BD or TDS for 3-4 weeks; less effective than a albendazole.

Mebendazole is one of the preferred drugs for treatment multiples infestations and is more effective than albendazole in trichuriasis. It has also been used for mass treatment, but need for multiple doses are a draw back. Reproduction in the extraction period for dracontiasis can be achieved by extended treatment with mebendazole.

Table 1: Choice of drugs for Helminthiasis

S/n	Worm	First Choice Drugs	Alternatives
1	ROUND WORM Ascaris lumbricoides	Mebendazole Albendazole Pyrantel	Piperazine, Tetramisole, Levamisole
2	HOOK WORM Ancylostoma duodenale Necator americanus	Pyrantel, Mebendazole, Albendazole Mebendazole, Albendazole	Levamisole Pyrantel
3	THREAD WORM Enterobius (Oxyuris vermicularis	Mebendazole Albendazole, Pyrantel	Piperazine
4	Strongyloides stercoralis	Thiabendazole	
5	WHIP WORM Trichuris trichiura	Mebendazole Albendazole	Albendazole, Pyrantel thiabendazole
6	Trichinella spiralis	Albendazole	Thiabendazole
7	FILARIA Wuchereria bancrofti, Brugia malayi	Diethyl carbamazine	Ivermectin
8	GUINEA WORM Dracunculus medinensis	Niridazole, Metronidazole	Thiabendazole
9	TAPE WORMS Taenia saginata Tenia solium Hymenolepis nana Neurocysticercosis	Niclosamide, praziquantel Praziquantel Nicolsamide, praziquantel Albendazole, praziquantel	Mebendazole, Albendazole Niclosamide, Mebendazole Albendazole
10	HYDATID DISEASE Echinococcus granulosus e.multilocularis	Albendazole	Mebedazole

Albendazole

It is a subsequently introduced congener of mebendazole: retains the broad spectrum activity and excellent tolerability of its predecessor, and has the advantage of single administration in many cases. One dose treatment has produced cure rates in ascariasis, hook worm (both species) and enterobiasis which are comparable to 3 day treatment with mebendazole. Results in trichuriasis have been inferior to mebendazole. In strongyloidosis it is more effective than mebendazole: a 3 day course has achieved nearly 50% cure, and a second course repeated after 3 weeks cured practically all patients. Three day treatment has been found to be necessary for tape worms including *H. nana*. Results in hydatid disease and hook worm have been superior to mebendazole is similar to that of mebendazole.

Absorption of albendazole after oral administration is moderate but inconsistent. The fraction absorbed is converted by first pass metabolism to its sulfoxide metabolite which is active in contrast to the metabolites of mebendazole and thiabendazole. Albendazole sulfoxide is widely distributed in the body, enters brain and is excreted in urine with a $t_{1/2}$ of 8.5 hours.

Albendazole is well tolerated; only gastrointestinal side effects have been noted. Few patients have felt dizziness. Prolonged use as in hydatid or in cysticercosis has caused headache, fever, alopecia, jaundice and neutropenia.

ZENTEL, ALMINTH, ALBENZOLE 400mg tab, 200mg/5ml suspension.

No preparation or postdrug fasting/purging is required.

- Ascaris, hook worm, Enterobius and Trichuris; a single dose of 400 mg (for adults and children above 2 yrs, 200 mg 1-2 yr age).
- Tape worms and strongyloidosis: 400 mg daily for 3 consecutive days.

- Trichinosis: three day treatment expels the adult worm from intestine, but has limited effect in larve that have migrated to muscles. They are not killed but symptomatic relief occurs. Corticosteroids are added if systemic manifestations are severe.
- Neurocysticercosis: One month treatment with 15 mg/kg daily has produced results equivalent to or better than praziquantel. In this condition albendazole now shares the drug of choice status with praziquantel and is much cheaper. A shorter 8day course of albendazole has also been found to be effective. With either drug corticosteroids are started before and continued through the initial days of the course to suppress the inflammatory reaction due to release of substances from the killed cysticerci. Cysticercosis of other tissues (muscles, subcutaneous area) also responds, but no drug should be given for ocular cysticercosis-blindness can occur due to the reaction.
- Hydatid disease: 400 mg BD for 4 weeks repeat after 2 weeks (if required) up to 3 courses. It is the preferred treatment for inoperable cases and before surgery.

Because it has exhibited embryotoxicity in animals, use in pregnant women is contraindicated. It should be give with caution to patients with hepatic or renal disease.

Thiabendazole

It was the first benzimidazole polyanthelmintic introduced in 1961, which covered practically all species of nematodes infesting the g.i.t-round worm, hook worm, Enterobius, Trichris, Strongyloides and Trichinella spiralis. It also inhibits development of the eggs of worms and kills larvae. Thiabendazole afford symptomatic relief in cutaneous larva migrans and skeletal muscle symptoms

produced by migration of *Trichinella spiralis* larvae to muscles. Symptomatic relief also occurs in guinea worm disease.

The mechanism of action of thiabendazole is the same as described for mebendazole. Thiabendazole has anti-inflammatory, analgesic and antipyretic actions. These may contribute to its effect cutaneous larva migrant and other inflammatory conditions produced by larvae or worms in tissues. However, it is ineffective in filariasis. Thiabendazole inhibits dermatophytic fungi also.

Pharmacokinetics: Thiabendazole is rapidly absorbed. It is metabolized by hydroxylation and conjugation to inactive metabolites and excreted in urine without cumulation.


Adverse effects: These are frequent and often interfere with normal activity. Nausea, vomiting, loss of appetite, headache, giddiness are most common. It can impair alertness-driving and operation of machinery should be prohibited. Itching, abdominal pain, diarrhea and a variety of other symptoms are also produced. Neurological symptoms, bradycardia, hypotension and liver damage are rare. Hypersensitivity symptoms consist of chills, fever, flushing, rashes and lymph node enlargement seen in sensitive individuals.

It should be avoided in pregnancy, liver and kidney disease.

Dose 25 mg/kg/day in two divided doses taken after meals. Tablets must be chewed;

MINTEZOL 0.5 g tab, 0.5g/5 ml susp. (30 ml bottle).

Uses: Because of frequent side effects and poor patient acceptability, thiabendazole is used only when other better tolerated drugs are ineffective. It may be used as an alternative to albendazole in:

1. Strongyloidosis
 2. Cutaneous larva migrans
 3. Trichinosis-intestinal
- 
- give a 2 day course. If inadequate, repeat after a gap of 2 days

Infestation and larvae in Muscles.

Trichinella larvae in muscles are often not killed, but symptomatic relief occurs quickly. Because of the availability of effective and better tolerated drug, thiabendazole is rarely used now for ascariasis, anacylostimiasis, trichuriasis, enterobiasis or their mixed infestation.

Pyrantel pamoate

It was introduced in 1969 for thread worm infestation in children; use soon extended to round worm and hook worm as well. Efficacy against Ascaris, Enterobius and Ancylostoma is high and comparable to that of mebendazole. Lower cure rates (about 60%) have been obtained in case of Necator infestation. It is less active against strongyloides and inactive against Trichuris and other worms. Pyrantel causes activation of nicotinic cholinergic receptors in the worms resulting in persistent depolarization-slowly developing contracture and spastic paralysis. Worms are then expelled. An anticholinesterase action has also demonstrated. Because piperazine causes hyperpolarization and flaccid paralysis, it antagonizes the action of pyrantel. Cholinergic receptors in mammalian skeletal muscle have very low affinity for pyrantel.

Only 10-15% of an oral dose of pyrantel pamoate is absorbed; this is partly metabolized and excreted in urine.

Adverse effects: Pyrantel pamoate is remarkably free of side effects: occasional g.i. symptoms, headache and dizziness is reported. It is tasteless, nonirritant; abnormal migration of worms is nor provoked. Its safety in pregnant women and in children below 2 years has not been established.

Use and administration: For Ascaris, Ancylostoma and Enterobius: a single dose of 10-15 mg/kg (max 1 g) is recommended. A 3 day course for Necator and for Strongyloides has been suggested.

No fasting, purging or other preparation of the patient is needed.

Piperazine

Introduced in 1950, it is a highly active drug against *Ascaris* and *Enterobius*; achieves almost 100% cure rates. However, it is now considered a second choice drug even for these worms. It blocks neuromuscular transmission in round worm by antagonizing Ach action and causing hyperpolarization-flaccid paralysis of the worm – worms are expelled alive and recover if placed in piperazine free medium. Therefore, often a purgative (senna) is given with it, but is not necessary. No fasting or patient preparation is required. Piperazine does not excite *Ascaris* to abnormal migration. It does not affect neuromuscular transmission in man, probably because of lack of affinity for mammalian nicotinic cholinergic receptors.

Pharmacokinetics: A considerable fraction of the oral dose of piperazine is absorbed. It is partly metabolized in liver and excreted in urine.

Adverse effect: Piperazine is safe and well tolerated. Nausea, vomiting, abdominal discomfort and urticaria are occasional.

Dizziness and excitement occur at high doses; toxic doses produce convulsions; death is due to respiratory failure. It is contraindicated in renal insufficiency and in epileptics, but is safe in the pregnant.

Preparations Piperazine is used either as its hexahydrate or salts like citrate, phosphate, adepter. All are water soluble and tasteless.

PIPERAZINE CITRATE, ANTEPAR 4.5 G (As Citrate) In 10 G Granules (With Sennoside 12 MG); 0.75 g/5 ml elixir in 30 ml, 115 ml bottle; 0.5 g (as phosphate) tablets; HELMACID 4 G (as phosphate) in 10 g granules with Cal. Sennosides 33 mg.

Combination of any other anthelmintic (except piperazine) with a purgative in the same formulation is banned in India.

Uses: For round worm infestation 4.5 g once a day for 2 consecutive days; children 0.75 g/year of age (max. 4.5g) is considered curative. Because of its capacity to relax ascarids, it is of particular value in intestinal obstruction due to round worms. It can be used during pregnancy while other drugs cannot be used. Enterobiasis – 50 mg/kg (max. 2.5g) once a day for 7 days or 75 mg/kg (max. 4.5 g)

Levamisole, Tetramisole

Tetramisole was developed in the late 1960s. It is racemic; its levo isomer (levamisole) was found to be more active and is preferred now. Both are active against many nematodes, but use is restricted to ascariasis and ancylostomiasis, because action on other worms is poor. It kills *Strongyloides* larvae, but adult worms are not sensitive. It stimulates the ganglia in worms, causes tonic paralysis which results in expulsion of live worms. Interference with carbohydrate metabolism may also be contributing.

Uses: For ascaris infestation a single dose of levamisole 50 mg for children 10-19 kg body weight, 100 mg for 20-39 kg and 150 mg for >40 kg and adults is advocated. It achieves > 90% cure rate. Owing to good tolerance and low dose, it has been successfully used in mass treatment of round worm.

It is an alternative drug for *A. duodenale*, 2 doses at 12 hour interval are suggested- achieves 70-90% cure. It is less efficacious against *Necator*.

Tetramisole: DECARIS 50, 150 mg tab

Levamisole: DEWORMIS, VERMISOL 50, 150 mg tab, 50 mg/5 ml syr.

Levamisole is an immunomodulator – restores depressed T cell function. It has been used as a disease modifying drug in rheumatoid arthritis and as an adjunct in

malignancies. It has also been tried in aphthous ulcers and recurrent herps, but repeated doses produce severe reactions; not used now.

Adverse effects: One or two doses used in helminthiasis are well tolerated. Incidence of side effects- nausea, abdominal pain, giddiness, fatigue, fatigue, drowsiness or insomnia is low.

4- Diethyl carbamazine citrate (DEC)

Developed in 1948, it is the only drug available for filariasis. DEC is absorbed after oral ingestion, distributed all over the body ($V=3-5L/kg$), metabolized in liver and excreted in urine. Excretion is faster in acidic urine. Plasma $t_{1/2}$ of usual clinical doses 12 hours.

Diethylcarbamazine has a highly selective effect on microfilariae (Mf). A dose of 2 mg/kg TDS clears Mf of *W.bancrofti* and *B. malayi* from peripheral blood in 7 days. However, Mf present in nodules and transudate (hydrocoele) are not killed. The most important action of DEC appears to be alteration of Mf membranes so that they are readily phagocytosed by tissue fixed monocytes, but not by circulating phagocytes. It also has an effect on the muscular activity of the Mf and adult worms so that they are dislodged. Prolonged treatment may kill adult *B. malayi* and probably *W. bancrofti* worms also.

DEC is active against Mf of *Loa loa* and *Onchocerca volvulus*. The adult worm of *L. loa* but not *O. volvulus* is also killed. It reduce worm burden in ascariasis, but efficacy is low.

Uses

1. **Filariasis:** 2 mg/kg TDS produces rapid symptomatic relief; Mf disappear from blood and patient become non-infective to mosquitoes in 7 days. However, the adult worm survives in the lymphatics and gives rise to intermittent microfilaremia and symptoms. Prolonged treatment with different schedules has been found to achieve radical cure in most

patients. A total dose of 72-126 mg/kg spread over 12 days to several weeks has been found to be satisfactory; more than one course may be needed with gap of 3-4 weeks. Elephantiasis due to chronic lymphatic obstruction is not affected by DEC.

2. Tropical eosinophilia: DEC (4 mg/kg DB-TDS) produces dramatic improvement in the signs and symptoms of eosinophilic lung or tropical eosinophilia. The benefit probably reflects anti-microfilarial action. The symptoms of the disease being presumably due to reaction to the Mf.

HETRAZAN, BANOCIDE 50, 100 mg tab, 120 mg/5 ml syr, 50 mg mg/5 ml pediatric syr.

Loa loa and *O. volvulus* infection can also be treated with DEC, but it is imperative to give small (25-50 mg) test dose initially.

Adverse effects: These are common but generally not serious. Nausea, loss of appetite, headache, weakness and dizziness are the usual complaints.

A febrile reaction with rash, pruritus, enlargement of lymph nodes and fall in BP may occur due to mass destruction of Mf and adult worms. This is usually mild, but may be severe. The reaction can be minimized by starting with a low dose (0.5 mg/kg). When it occurs. Subsequent administration of DEC does not cause any reaction. Leukocytosis and mild albuminuria are also noted.

Ivermectin: It is an extremely potent semisynthetic derivative of the antinematodal principle obtained from *Streptomyces avermitilis*, that is now the drug of choice for *O. volvulus*. It is not marketed in India, but where available it is the drug of choice for strongyloidosis, and an alternative drug for single dose treatment of *W. bancrofti*, *B. malayi*, *Ascaris*, *Enterobius* and *Trichuris* infestation. It is also effective in visceral larva migrans. Nematodes develop tonic paralysis when exposed to ivermectin. This is believed to be due to potentiation of GABAergic transmission in the worm, but recent evidence

points to action through a special type of glutamate gated Cl channel in the susceptible worms. Such channels are not involved in the motor control of cestodes and trematodes, they are unaffected by ivermectin. The lack of GABA related actions in man is explained by its low affinity for mammalian GABA receptors and its inability to penetrate the blood-brain barrier.

A single 10-15 mg oral dose of ivermectin produces long lasting reduction of Mf counts in onchocerciasis without affecting the adult worm. Though it does not cure the condition, ocular inflammation and damage, as well as lymphadenopathy are suppressed with only mild systemic or ocular reactions. It has therefore replaced DEC for onchocerciasis and has been used in the onchocerciasis (river blindness) control programme of WHO. Side effects to ivermectin have been mild-pruritus- giddiness and transient ECG changes but more important are the reactions due to degradation products of the microfilariae.

In 1960s, niclosamide was shown to be a highly effective drug against cestodes
Niclosamide

infesting man-Taenia saginata, T. solium, Diphyllbothrium latum and Hymenolepis nana, as well as thread worm. The drug appears to act by inhibiting oxidative phosphorylation in mitochondria and interfering with anaerobic generation of ATP by the tape worm. Injured by niclosamide, the tape worms are partly digested in the intestine. In cases of T. solium, digestion of the dead segments can be hazardous, because the ova released from them may develop into larvae in the intestine, penetrate its wall and cause visceral cysticercosis.

Regimen for tape worm: Niclosamide is available as 0.5 g tabl (NICLOSAN, NICLOTAPE). After a light breakfast, 2 tablets are to be chewed and swallowed with water, followed by another 2 tablets after 1 hr (total 2 g); total dose for children 2-6 years is 1 g. A saline purge is given 2 hours after the

laster dose to wash off the worm. The scolex should be searched in the stools to be sure that the worm will not grow again. A thorough purge is essential in the cases of *T. solium* so that all segments are passed out and cysticercosis does not occur. Because praziquantel does not lead to digestion of the worm and kills encysted larvae as well, it is being preferred over niclosamide in cases of *T. solium* infestation.

For *H. nana* the 2 g dose is repeated daily for 5 days. This is needed because the cysticerci of *H. nana* (which are not affected by niclosamide) develop in the jejunal villi of the same host and worms appear in the intestinal lumen after 4 days. However, no purgative is required. In some cases treatment may have to be repeated after 10 days.

Adverse effects: Niclosamide is tasteless and nonirritating. It is minimally absorbed from g.i.t.- no systemic toxicity occurs. It is well tolerated; minor abdominal symptoms are produced occasionally. Malaise, pruritus and light headedness are rare. Niclosamide is safe during pregnancy and in patients with poor health.

Niridazole: It is a nitrothiazole; highly active against schistosomes, guinea worm, entamoeba, anaerobic bacteria and has anti-inflammatory property. It inhibits glucose uptake by parasites. It is absorbed after oral administration; undergoes high first pass metabolism in liver, and is excreted in urine and faeces.

It is the drug of choice in guinea worm infestation 1-1.5 g (children 25 mg/kg) daily for 7 days produces marked symptomatic relief. The worm is either extruded spontaneously or can be extracted more easily from its subcutaneous location, after the course of treatment. No reaction occurs even if the worm breaks while extracting. Niridazole produces a number of side effects and toxicities-specially involving cardiovascular and central nervous systems. It also has carcinogenic potential.

Metronidazole (200-400 mg TDS x 7 days) produce similar results and is used in India because niridazole is not available.

Praziquantel

It is a significant recent addition having wide ranging activity against Schistosomes, other trematodes, cestodes and their larval forms but not nematodes. It is rapidly taken up by the susceptible worms and appears to act by causing leakage of intracellular calcium from the membranes- contracture and paralysis. The tape worms lose grip of the intestinal mucosa and are expelled. Flukes are also dislodged. Praziquantel is active against adult as well as juvenile and larval stages of tape worms.

At relatively higher concentrations, it causes vacuolization of the tegument and release of the contents of the worms and flukes followed by their destruction by the host. This action appears to be more important in the cases of Schistosomes and flukes.

Pharmacokinetics: Praziquantel is rapidly absorbed from intestines and undergoes high first pass metabolism in liver which limits its systemic bioavailability. Phenytoin, Carbamazepine and possibly dexamethasone induce praziquantel metabolism and further reduce its bioavailability. Patients of neurocysticercosis are often receiving these drugs –may contribute to therapeutic failure of praziquantel. It crosses blood-brain barrier and attains therapeutic concentrations in the brain and CSF. The plasma $t_{1/2}$ is short (1.5 hours). Adverse effects: Despite systemic absorption, praziquantel has exhibited no systemic toxicity. It tastes bitter, can produce nausea and abdominal pain. Other side effects are headache, dizziness and sedation. When used for schistosomes and visceral flukes, symptoms like itching urticaria, rashes, fever and bodyache occur as a reaction to the destroyed parasites.

No interaction with food, alcohol or tobacco has been noted.

Uses

1. **Tapeworms:** Praziquantel administered as a single dose has achieved 90-100% cure rate in all human tape worms. This level of activity is similar to that of niclosamide and even better in case of *H. nana*.

T. saginata, *T. solium*; 10 mg/kg single dose in morning. It is specially valuable in case of *T. solium*, because it kills the tape worm larvae within the cysts and there are no chances of systemic cysticercosis developing.

H. nana, *D. latum*: 15-25 mg/kg single in morning. This is much simpler compared to 5 day treatment needed with niclosamide for eradication of *H. nana*. In case of heavy infestation, retreatment after one week is desirable.

2. **Neurocysticercosis:** Praziquantel was the first drug found to be effective in neurocysticercosis: 50 mg/kg daily in 3 divided doses for 15 days kills the larvae lodged in brain and other tissue. Now albendazole has been shown to be equally or more effective; both drugs are being used as first line therapy (see p. 818). It is also effective in dermal cysticercosis, but contraindicated in ocular cysticercosis.

3. **Schistosomes:** All 3 species can be treated with 40-75 mg/kg given once or in installments in one day.

4. **Other flukes:** Praziquantel is the drug of choice for all schistosome and fluke infestations except *Fasciola hepatica*. The flukes respond to 75 mg/kg/day given for one day in most and two days in some cases.

CYSTICIDE 500 mg tab.

Praziquantel is thus a drug with unique efficacy and good tolerability; but its high cost is a limiting factor.

