Pharmacology of anthelmintics: albendazole, mebendazole and praziquantel

Parasitic helminthic infections are an important cause of morbidity and mortality worldwide. The helminths include soil-transmitted intestinal nematodes (roundworms), trematodes (flukes) and cestodes (tapeworms) (Table I).

The disease burden caused by worm infestation is unevenly distributed, with low-income countries being the worst affected. The most heavily infested persons are at the highest risk of morbidity and are the major source of environmental contamination and further transmission. In low-income countries, soil-transmitted helminths are one of the most important causes of growth and mental retardation, and neurocysticercosis is the main cause of adult-onset epilepsy (other than trauma). In pregnancy, severe iron deficiency anaemia due to hookworm infestation can result in poor maternal, fetal and neonatal outcomes.

Albendazole, mebendazole and praziquantel are the only available anthelmintics in our essential medicines list. These drugs have broad-spectrum coverage with high cure rates. However, re-infection is very common. Specific population groups (preschool and school-age children, adolescent girls and pregnant women) have been targeted for mass treatment campaigns to reduce transmission rates. The school-based national control programmes have been shown to decrease transmission and to improve growth and cognitive performance in children. Intervention studies in pregnant women have also shown that antenatal anthelmintics in the second trimester led to a substantial increase in maternal haemoglobin and an improvement in neonatal outcomes. However, there have been concerns regarding the sustainability of periodic de-worming and the emergence of resistance.

This review briefly discusses the common helminth infections and focuses on the pharmacology of the few drugs available to treat them (albendazole, mebendazole and praziquantel).

Table I. Common helminth infections and their complications

Major pathogens	Disease	Complications
Intestinal nematodes (roundworms)		
Ascaris lumbricoides	Ascariasis (common roundworm infection)	Lactose intolerance, vitamin A malabsorption, intestinal obstruction, hepatopancreatic disease
		Growth and mental retardation
Trichuris trichiura	Trichuriasis (whipworm infection)	Colitis, *Trichuris* dysentery syndrome, anaemia, rectal prolapse
Necator americanus or *Ancylostoma duodenale*	Hookworm infection	Intestinal blood loss, iron deficiency anaemia, protein malnutrition
Enterobius vermicularis	Enterobiasis (pinworm infection)	Perianal/perineal itch with subsequent scratching and excoriation, and bacterial superinfection
Toxocara canis (dog) or *Toxocara cati* (cat)	Toxocariasis: visceral larva migrans (usually liver and lungs, rarely brain) and ocular larva migrans	Hepatitis and pneumonitis, meningoencephalitis, cerebritis, seizures, blindness
Trematodes (flukes)		
Schistosoma mansoni and *Schistosoma haematobium*	Intestinal and urinary (bilharzia) schistosomiasis	Pulmonary and portal hypertension, haematuria, obstructive uropathy, bladder cancer, spinal cord granulomas
Cestodes (tapeworms)		
Taenia saginata (beef) and *Taenia solium* (pork)	Taeniasis or cysticercosis	Appendicitis, cholangitis Acquired adult-onset epilepsy
Echinococcus granulosus	Hydatid disease	Hepatic, pulmonary or spinal brain hydatid cycts

Common helminth infections

Roundworms

Soil-transmitted helminths are a group that cause human infection through skin contact with eggs or larvae that thrive in warm and moist soil in tropical or subtropical areas. Migration of the larval forms of some helminths may cause cutaneous larva migrans or systemic features, usually including pulmonary involvement, with eosinophilia (known as visceral larva migrans). Surgical complications may occur owing to intestinal obstruction (Table I). Mixed infection with intestinal worms (*Ascaris lumbricoides, Trichuris trichiura* and *Necator americanus* or *Ancylostoma duodenale*) is very common, with evidence of household aggregation of infection.

Enterobiasis is caused by the human pinworm *Enterobius vermicularis.* Humans are the only host. Enterobiasis seldom causes serious clinical disease. Eggs are deposited on perianal folds. Self-infection occurs by transferring infective eggs to the mouth with hands that have scratched the perianal area. After ingestion of infective eggs, the larvae hatch in the small intestine and the adults establish themselves in the colon. Gravid females migrate nocturnally outside the anus and deposit eggs while crawling on the skin of the perianal area. Person-to-person transmission can also occur through handling of contaminated clothes or bedlinen.

Enterobiasis may also be acquired through surfaces that are contaminated with pinworm eggs (e.g. curtains, carpets). A small number of eggs may become airborne and be inhaled. These would be swallowed and follow the same development as ingested eggs. Retro-infection (migration of larvae from the anus back to the rectum) may also occur.

Toxocariasis results from zoonotic transmission of the roundworms *Toxocara canis* and *T. cati* from dogs and cats, respectively. Humans are the accidental hosts and infection is caused by ingestion of eggs containing larvae shed in dog and cat faeces by hand to mouth contact. After ingestion the eggs release larvae that penetrate the stomach and migrate through the liver, lungs and central nervous system, causing mechanical and immunological damage to the tissues (Table I). The host inflammatory response that follows usually kills the larvae or forces them into arrested development.

Flukes

Schistosoma (trematode) infections are transmitted after direct contact with fresh water harbouring free-swimming larval forms of the parasites. They penetrate intact human skin and enter capillaries and then migrate to the portal venous system where they mature and unite. Acute schistosomiasis, also known as Katayama fever, is a form of visceral larva migrans. The adult male and female pairs ultimately migrate to the superior mesenteric veins (*S. mansoni*) and vesical and ureteric veins (*S. haematobium*). The eggs are shed in the faeces and urine and transmission continues. Haematuria is a common presentation but patients may present with hepatosplenic schistosomiasis without prior intestinal symptoms (Table I).

Tapeworms

Taeniasis is spread by ingestion of raw or undercooked beef (*Taenia saginata*) or pork (*T. solium*) infected with cysticerci. Humans are the definitive hosts. After ingestion of infected beef or pork in the intestine the cysticercus develops over 2 months into an adult tapeworm, which can survive for years. Intestinal taeniasis is usually asymptomatic or produces mild abdominal symptoms. Patients may also report the passage of proglottids in the stool.

Humans may act as intermediate hosts for *T. solium*, with the development of tissue cysts (cysticercosis). Neurocysticercosis is the infestation of the central nervous system and its coverings by the larval stage of the pork tapeworm *T. solium*. It is the most common helminthic infestation of the central nervous system and is a leading cause of acquired epilepsy worldwide. Diagnosis has improved with neuro-imaging. Medical treatment (albendazole or praziquantel) and occasionally surgical treatment are complementary in carefully selected cases.

Hydatid disease is a zoonotic infection caused by *Echinococcus granulosus*. Domestic dogs are definitive hosts, sheep are usually the intermediate hosts and humans may be accidental intermediate hosts. Human infection occurs when eggs are accidentally ingested. The larvae invade tissues and develop in internal organs to form cysts of varying sizes (usually 1 - 15 cm in diameter). Slow-growing solitary cysts are common, but multiple cysts can occur. The liver and lungs are predominantly affected, but any system can be involved including the central nervous system and musculoskeletal system. Morbidity depends on the number, size, and developmental status of the cyst, the involved organ, the localisation of the cyst within the organ, pressure effects of the cyst and the host defence mechanism. The definitive treatment is by percutaneous aspiration and injection of scolicidal agents, followed by re-aspiration. This has largely replaced surgery, which carries the risk of perioperative morbidity, recurrence of cysts, and spillage of hydatid fluid from the cysts, which can lead to anaphylaxis and dissemination of infection. Adjunctive medical therapy is used before aspiration or surgery, or in cases not suitable for either procedure, and is discussed below.

Treatment of helminthic infections

Anthelmintic drugs have a broad spectrum of activity. They can be used as a single dose for several infections and are generally well tolerated. Briefly discussed below is the pharmacology of the widely used anthelmintics i.e. albendazole, mebendazole and praziquantel (Table II).

Albendazole and mebendazole–benzimidazole derivatives

Mebendazole and albendazole are benzimidazole derivatives. The mechanism of action is blocking glucose uptake in susceptible helminths, thus depleting energy

Table II. Recommended anthelmintic dosing regimen for various indications (adapted from the *South African Medicines Formulary*, 8th ed., 2008)

Drug	Infection	Dosing regimen (oral route)
Albendazole	Roundworm, hookworm and pinworm	200 mg single dose in children 1 - 2 yrs
		400 mg single dose in child >2 yrs or adult
	Whipworm Taeniasis (intestinal)	400 mg daily for 3 days, may repeat after 3 weeks
	Toxocariasis	5 - 10 mg/kg for 5 days
	Hydatid disease	400 mg twice daily (or 10 - 15 mg/kg/d) for 3 - 6 months
	Neurocysticercosis	15 mg/kg/d in 3 divided doses for 14 days
Mebendazole	Roundworm, pinworm and whipworm	100 mg twice daily for 3 days or 500 mg as a single dose, repeat after 3 - 4 weeks if necessary
	Pinworm	100 mg single dose, repeated after 2 weeks if necessary
	Hookworm infection	100 mg twice daily for 3 days
	Toxocariasis	100 - 200 mg twice daily for 5 days
	Taeniasis (intestinal)	100 mg twice daily for 6 days
Praziquantel	Schistosomiasis	40 mg/kg as single dose or in 2 divided doses
	Intestinal taeniasis	5 - 10 mg/kg as a single dose
	Cysticercosis	50 mg/kg in 3 divided doses for 14 days

required for their survival. They are useful in single doses for mixed intestinal worm infections as they have a broad spectrum. For example, a recent meta-analysis by Keiser showed that single doses of albendazole and mebendazole have high cure rates (88 - 95%) for ascariasis. For hookworm infections, albendazole was more efficacious than mebendazole; hence a longer course of the latter is recommended (Table II). Cure rates for trichuriasis with single-dose regimens are low – 28% (95% CI 13 - 39%) and 36% (95% CI 16 - 51%) for albendazole and mebendazole, respectively.

Albendazole has a wider spectrum than mebendazole, being effective against strongyloidiasis, toxocariasis, hydatid disease, and cysticercosis. Of note, when albendazole is used for neurocysticercosis or ocular cysticercosis, concomitant steroid therapy with strict supervision may be indicated to reduce the host inflammatory response to the death of the parasite. The use of anthelmintic drugs for therapy of neurocysticercosis results in better resolution of viable parenchymal cysts and lower risk of recurrence, and reduces seizure frequency when compared with placebo. In hydatid disease, albendazole reduces the viability of protoscolices and cysts. Its active metabolite is active against the larval cestodes. Drug therapy is indicated in inoperable cases (where long-term therapy is used), spontaneous or operative rupture of the cyst, or before and after aspiration and surgery.

There are limited data in children under 1 year of age. In children older than a year, treatment with single doses showed improvement in physical and intellectual growth. Animal studies showed teratogenicity; these drugs are therefore contraindicated in the first trimester. However, the benefits almost certainly outweigh the risks when treatment is given after the first trimester.

Both albendazole and mebendazole are generally well tolerated in doses recommended for intestinal worms. Gastrointestinal discomfort has been reported. When prolonged therapy or higher doses of albendazole are used for hydatid disease or cysticercosis leucopenia, abnormalities in liver functions, allergic reactions and alopecia have been reported. Regular monitoring of the alanine transaminase and white cell count should be done.

Praziquantel – pyrazinoisoquinoline derivative

Praziquantel is a pyrazinoisoquinoline derivative whose mechanism of action is the increase in muscular activity, causing contraction and spastic paralysis of the parasite. It also causes tegumental damage of the susceptible parasite.

It is the agent of choice for schistosomiasis and can be used as a single dose, with high cure rates and substantial reduction of the worm burden and egg production. It is also useful for intestinal tapeworm infections (taeniasis). Praziquantel has been used for neurocysticercosis, but the duration of therapy is longer than with albendazole, which most experts now prefer.

Praziquantel can be safely used in children older than 2 years. Risk-benefit analysis of its use for schistosomiasis in pregnancy suggests that treatment should be offered on an individual basis and pregnant women should be included in mass treatment campaigns.

The adverse effects are usually mild and transient. However, when used in neurocysticercosis inflammatory response to dead and dying parasites may lead to fever, cerebral oedema, raised intracranial pressure and convulsion.

Conclusion

To summarise, albendazole, the newer benzimidazole derivative, is effective against most intestinal nematode and cestode infections and is, therefore, the drug of choice in mixed worm infection. When prescribed as a single dose for treating hookworm infection, it is better than mebendazole. It is a useful adjunct in hydatid disease. It is also more effective than praziquantel in neurocysticercosis. Mebendazole also has a broad spectrum against intestinal nematodes. Both have lower efficacy against trichuriasis. Praziquantel is the drug of choice for schistosomiasis and is also effective against intestinal taeniasis and neurocysticercosis.

Despite the high cure rates re-infection is very high and preventive measures are necessary. These include: improving basic sanitation, proper hygiene education, wearing shoes, treatment of all household members, periodic mass treatment of targeted population groups and de-worming of livestock and domestic animals.

Further reading

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PHUMLA SINXADI, *MB ChB, DA (SA)*
GARY MAARTENS, *MB ChB, MMed, FCP (SA), DTM&H*

Division of Clinical Pharmacology
Department of Medicine
University of Cape Town

Corresponding author: Phumla Sinxadi (phumla.sinxadi@uct.ac.za)

In a nutshell

- Albendazole and mebendazole are broad-spectum anthelmintics effective against soil-transmitted helminths.
- Albendazole has an extended spectrum against tapeworm infection and is therefore the drug of choice in mixed infestation.
- Praziquantel is the drug of choice for schistomiasis.
- Praziquantel or albendazole results in better resolution of viable parenchymal cysts and less recurrence of cysts, and reduced frequency of seizures in neurocysticercosis.
- Mass treatment campaigns with single doses of albendazole or mebendazole or praziquantel are important tools for reducing the disease burden caused by helminths.
- Preventive measures reduce transmission and must be emphasised.