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).

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.

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

Table I. Common helminth infections and their complications
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, caused by *S. mansoni* and *S. haematobium*, and the development of tissue cysts (cystercerosis). 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.

**Hookworm infection**

Toxocariasis

**Praziquantel**

It is the infestation of the central nervous system by the cysticerci (parasitic larval stages of *Cysticercus cuniculi*), 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.

**Toxocariasis**

**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 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 localization 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.

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

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
cascarisis. 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, toxocarasis, hydatid
disease, and cisticercosis. Of note, when
albendazole is used for neurocysticercosis
or ocular cisticercosis, 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 cisticercosis 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
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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In a nutshell

• Albendazole and mebendazole are broad-spectrum 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 schistosomiasis.
• 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.