Anthelmintic Drugs

**I. OVERVIEW**

Three major groups of helminths (worms), nematodes, trematod, and cestodes, infect humans. As in all antibiotic regimens, the anthelmintic drugs (Figure 37.1) are aimed at metabolic targets that are present in the parasite but are either absent from or have different characteristics than those of the host. Figure 37.2 illustrates the high incidence of helmintic infections.

**II. DRUGS FOR THE TREATMENT OF NEMATODES**

Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus. They cause infections of the intestine as well as the blood and tissues.

1. **Mebendazole**

Mebendazole [me-BEN-da-zole], a synthetic benzimidazole com- pound, is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (Trichuris trichiura), pinworm (Enterobius vermicularis), hookworms (Necator ameri- canus and Ancylostoma duodenale), and roundworm (Ascaris lum- bricoides). Mebendazole acts by binding to and interfering with the assembly of the parasites’ microtubules and also by decreasing glucose uptake. Affected parasites are expelled with feces. Mebendazole is nearly insoluble in aqueous solution. Little of an oral dose (that is chewed) is absorbed, unless it is taken with a high-fat meal. It under- goes first-pass metabolism to inactive compounds. Mebendazole is relatively free of toxic effects, although patients may complain of abdominal pain and diarrhea. It is, however, contraindicated in pregnant women (Figure 37.3), because it has been shown to be embryo- toxic and teratogenic in experimental animals.

1. **Pyrantel pamoate**

Pyrantel pamoate [pi-RAN-tel PAM-oh-ate], along with mebendazole, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms (Figure 37.4). Pyrantel pamoate is poorly absorbed orally and exerts its effects in the intestinal tract. It acts as a depolarizing, neuromuscular-blocking agent, causing persistent activation of the parasite’s nicotinic receptors. The paralyzed worm is then expelled from the host’s intestinal tract. Adverse effects are mild and include nausea, vomiting, and diarrhea.

1. **Thiabendazole**

Thiabendazole [thye-a-BEN-da-zole], another synthetic benzimidazole, is effective against strongyloidiasis caused by Strongyloides stercora- lis (threadworm), cutaneous larva migrans, and early stages of trichinosis (caused by Trichinella spiralis; see Figure 37.4). Thiabendazole, like the other benzimidazoles, affects microtubular aggregation. Although nearly insoluble in water, the drug is readily absorbed on oral administration. It is hydroxylated in the liver and excreted in urine. The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting. There have been reports of central nervous system (CNS) symptomatology. There have been a number of fatalities among the cases of erythema multiforme and Stevens-Johnson syndrome reportedly caused by thiabendazole. Its use is contraindicated during pregnancy.

1. **Ivermectin**

Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by Onchocerca volvulus and for cutaneous larva migrans and strongyloidiasis. Ivermectin targets the parasite’s glutamate-gated chloride channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm. The drug is given orally. It does not cross the blood-brain barrier and has no pharmacologic effects in the CNS. However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable, making CNS effects possible. Ivermectin is also contraindicated in pregnancy (see Figure 37.3). The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, and hypotension).

1. **Diethylcarbamazine**

Diethylcarbamazine [dye-eth-il-kar-BAM-a-zeen] is used in the treatment of filariasis because of its ability to immobilize microfilariae and render them susceptible to host defense mechanisms. Combined with albendazole, diethylcarbamazine is effective in the treatment of Wuchereria bancrofti and Brugia malayi infections. It is rapidly absorbed following oral administration with meals and is excreted primarily in urine. Urinary alkalosis and renal impairment may require dosage reduction. Adverse effects are primarily caused by host reactions to the killed organisms. Symptoms include fever, malaise, rash, myalgias, arthralgias, and head- ache, and their severity is related to parasite load. Most patients have leucocytosis. Antihistamines or steroids may be given to ameliorate many of the symptoms. Figure 37.4 summarizes the major infections caused by nematodes and the common therapies for them.

**III. DRUGS FOR THE TREATMENT OF TREMATODES**

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect. For example, they may be categorized as liver, lung, intestinal, or blood flukes (Figure 37.5).

1. **Praziquantel** Trematode infections are generally treated with praziquantel [pray- zi-KWON-tel]. This drug is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis. Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite. Praziquantel is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid. High levels occur in bile. The drug is extensively metabolized oxidatively, resulting in a short half-life. The metabolites are inactive and are excreted through urine and bile. Common adverse effects include drowsiness, dizziness, malaise, and anorexia as well as gastrointestinal upsets. The drug is not recommended for pregnant women or nursing mothers. Drug interactions due to increased metabolism have been reported with dexamethasone, phenytoin, and carbamazepine. Cimetidine, which inhibits cytochrome P450 isozymes, causes increased praziquantel levels. Praziquantel is contraindicated for the treatment of ocular cysticercosis, because destruction of the organ- ism in the eye may damage the organ.

**IV. DRUGS FOR THE TREATMENT OF CESTODES**

The cestodes, or “true tapeworms,” typically have a fl at, segmented body and attach to the host’s intestine (Figure 37.6). Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

1. **Niclosamide**

Niclosamide [ni-KLOE-sa-mide] is the drug of choice for most cestode (tapeworm) infections. Its action has been ascribed to inhibition of the parasite’s mitochondrial phosphorylation of adenosine diphosphate, which produces usable energy in the form of adenosine triphosphate. Anaerobic metabolism may also be inhibited. The drug is lethal for the cestode’s scolex and segments of cestodes but not for the ova. A laxative is administered prior to oral administration of niclosamide. This is done to purge the bowel of all dead segments and so preclude digestion and liberation of the ova, which may lead to cysticercosis. Alcohol should be avoided within 1 day of niclosamide.

1. **Albendazole**

Albendazole [al-BEN-da-zole] is a benzimidazole that, like the others, inhibits microtubule synthesis and glucose uptake in nematodes. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis (caused by Taeniasolium larvae) and hydatid disease (caused by Echinococcus granulosus). Albendazole is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism, including formation of the sulfoxide, which is also active. Albendazole and its metabolites are primarily excreted in urine. When used in short-course therapy (1–3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nau- sea. Treatment of hydatid disease (3 months) has a risk of hepatotoxic- ity and, rarely, agranulocytosis or pancytopenia. Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the CNS, including headache, vomiting, hyperthermia, convulsions, and mental changes. The drug should not be given during pregnancy (see Figure 37.3) or to children under 2 years of age.