

Antiprotozoal drugs

A. Benzimidazoles

Fenbendazole and Albendazole

Benzimidazoles bind to β -tubulin within a variety of helminths and protozoa. This leads to inhibition of tubulin polymerization and the formation of microtubules, with impaired cell division. Glucose uptake by parasites is also impaired. Resistance can result from production of altered β -tubulin by parasites, which reduces binding of benzimidazole drugs.

Fenbendazole

Fenbendazole is widely used to treat giardiasis in dogs and cats. It is safer than metronidazole, can be administered to young animals, and has higher efficacy, although treatment failure can still occur. A second course of treatment or administration of fenbendazole in combination with metronidazole can be effective in refractory cases. Administration with food may improve absorption, but the fat content of the food does not influence absorption. Adverse effects of fenbendazole are very rare but can include decreased appetite, vomiting, diarrhea, and rarely reversible pancytopenia. At high doses used to treat *Mesocostoides* spp. peritonitis (100 mg/kg q12h), neurologic signs have been observed. Febantel is metabolized to a benzimidazole compound and has been used in combination with praziquantel and pyrantel (Drontal Plus) to treat *Giardia* spp. infection in dogs, although efficacy at label dosages has been variable and some dogs can re-shed low numbers of cysts when treatment is discontinued.

Albendazole

Albendazole has an affinity for rapidly dividing cells, and although it is used extensively for treatment of parasitic infections in human patients, it has been associated with anorexia and reversible bone marrow suppression in dogs and cats especially when high doses are administered for more than 5 days. As a result, fenbendazole is used more commonly in small animals.

B. Nitroimidazoles

Protozoa reduce nitroimidazoles to nitro anion free radicals, which cause damage to parasite DNA. Some nitroimidazoles are mutagens and carcinogens, but carcinogenesis has not been demonstrated in dogs and cats with long-term use. Metronidazole, ronidazole, and tinidazole have primarily been used to treat enteric protozoal infections. Benzimidazole is specifically used to treat infections with *Trypanosoma cruzi*.

C. Metronidazole

Metronidazole is used to treat giardiasis in dogs and cats, although efficacy may be as low as 50%. It also has activity against amoebic infections. The clinical use and adverse effects of metronidazole are described in Chapter 8. Doses of metronidazole used for treatment of giardiasis have the potential to be associated with neurotoxicity, so fenbendazole is preferred because of greater safety and efficacy. Metronidazole can be combined with fenbendazole for refractory giardiasis.

D. Tinidazole

Tinidazole is a 5-nitroimidazole that has amoebicidal, giardicidal, trichomonocidal, and anaerobic bactericidal activity. It is sometimes used as a single-dose treatment for giardiasis in human patients. The efficacy of tinidazole for treatment for giardiasis in dogs and cats has not been evaluated, and the half-life in dogs (4.4 hours) and cats (8.4 hours) is shorter than that in human patients (>12 hours). Tinidazole is

very well absorbed in dogs and cats, with a bioavailability of 100%. Adverse effects are similar to those of metronidazole. Like metronidazole, tinidazole has a bitter taste.

E. Ronidazole

Ronidazole is the drug of choice for treatment of *Tritrichomonas foetus* infections, which are less responsive to metronidazole and tinidazole. Resistance to ronidazole has been identified in some isolates of *T. foetus* and is associated with treatment failure in infected cats. Resistance is thought to result from increased oxygen-scavenging capacity by the parasite, whereby oxygen competes effectively with ronidazole and other nitroimidazoles for ferredoxin-bound electrons.

Ronidazole is absorbed rapidly and completely after oral administration to cats. Some compounded formulations may have decreased efficacy as a result of low ronidazole content or differences in drug release at the site of action (the large bowel). A modified-release formulation that is delivered to the colon may have improved efficacy. Decreased appetite, vomiting, and neurologic signs can occur in dogs and cats, especially at doses above 30 mg/kg q12h in cats and at doses as low as 10 mg/kg/d in dogs. Once daily dosing is probably sufficient because of the long half-life of the drug in cats. Doses of 20 mg/kg or less may not effectively clear infection with *T. foetus*. Neurologic signs result from γ -aminobutyric acid (GABA) antagonism in the CNS and include ataxia, decreased mentation, agitation, tremors, and hyperesthesia, which occur up to 9 days after the start of treatment and resolve when the drug is discontinued.

F. Nitazoxanide

Nitazoxanide is a nitrothiazolyl-salicylamide derivative that has activity against *Giardia spp.*, *Cryptosporidium spp.*, *Sarcocystis neurona*, some anaerobic bacteria, *Helicobacter spp.*, and *Campylobacter jejuni*. It inhibits the pyruvate-ferredoxin/ferredoxin oxidoreductase enzyme-dependent electron transfer reaction that is essential for anaerobic metabolism in these organisms. Resistance has been documented in *Giardia spp.*

Reports of nitazoxanide use in dogs and cats have been rare, and its efficacy in dogs and cats is largely unknown. An equine formulation (Navigator) that was used to treat equine protozoal meningoencephalitis caused by *Sarcocystis neurona* has been removed from the market. Doses have been extrapolated from those used for human patients. Nitazoxanide treatment of cats co-infected with *Cryptosporidium spp.* and *T. foetus* led to cessation of shedding during treatment, but infection was not eliminated. Vomiting occurred frequently, especially at higher doses (75 mg/kg PO q12h). In humans, nitazoxanide is rapidly absorbed from the gastrointestinal tract and metabolized to the active metabolite tizoxanide, which is highly protein bound. After hepatic glucuronidation, it is excreted in urine and bile.

Antibacterial Drugs with Broad-Spectrum Antiprotozoal Activity

Folic Acid Antagonists

Trimethoprim, pyrimethamine, ormetoprim, and sulfadiazine inhibit parasite replication through folate antagonism. Synergistic combinations of sulfadiazine with trimethoprim or pyrimethamine are primarily used to treat toxoplasmosis, neosporosis, and intestinal coccidiosis (*Isospora spp.* infections) in dogs and

cats. A combination of pyrimethamine, trimethoprim-sulfadiazine, and clindamycin has also been used to treat *Hepatozoon americanum* infections.

Pyrimethamine

Like trimethoprim, pyrimethamine inhibits dihydrofolate reductase, which is necessary for synthesis of thymidine. However, in contrast to trimethoprim, it has a greater affinity for the protozoal enzyme than the bacterial enzyme. Resistance to pyrimethamine can occur when parasites synthesize dihydrofolate reductase enzymes with an altered drug target site. Pyrimethamine is well absorbed after oral administration and penetrates a variety of tissues including the CNS. Hepatic metabolism and some renal excretion occur. Although clearance of pyrimethamine is not affected by renal disease, the use of caution with hepatic or renal insufficiency has been recommended in human patients.

Pyrimethamine is well tolerated. Gastrointestinal signs such as vomiting, diarrhea, and decreased appetite occur in some treated animals. Bone marrow suppression can occur with prolonged treatment at higher doses as a result of folic acid deficiency. In human patients, concurrent administration of folinic acid is recommended when high doses are used for treatment of toxoplasmosis. Folinic acid, but not folic acid supplementation also reverses marrow suppression in dogs treated with pyrimethamine. The CBC should be monitored weekly during treatment, and supplementation should be provided if leukopenia develops and continued treatment is necessary. Stomatitis, ulcerative glossitis, and exfoliative dermatitis have also been described in human patients as a result of folic acid deficiency. Other adverse effects of pyrimethamine-sulfadiazine combinations result from the sulfadiazine component.

Unlike trimethoprim-sulfadiazine, there are no approved formulations of pyrimethamine-sulfonamides for dogs and cats. Pyrimethamine is available as a single agent in tablets but should be administered with a sulfonamide for the best efficacy. Another alternative is the combination of pyrimethamine-sulfadiazine, which is available in an oral liquid suspension for horses (ReBalance). Although off-label, it is a convenient formulation for small animal veterinarians. This formulation can be administered at a dose of 1 mg/kg pyrimethamine + 20 mg/kg sulfadiazine PO q24h. This is equivalent to 0.33 mL of the equine formulation per 4 kg of body weight for dogs and cats.

Macrolides And Lincosamides

Clindamycin, azithromycin, and clarithromycin have antiprotozoal activity. Clindamycin is the most widely used antiprotozoal for treatment of toxoplasmosis and neosporosis in dogs and cats. Although clindamycin inhibits shedding of *Toxoplasma gondii* oocysts by cats, clinical efficacy of clindamycin for treating toxoplasmosis in dogs and cats has been questioned by experts and in published studies. Trimethoprim-sulfonamides are a suitable alternative, or if clindamycin is used, pyrimethamine may be used in combination. In human patients, pyrimethamine and clindamycin are used as a substitute for pyrimethamine and sulfadiazine for treatment of toxoplasmosis in sulfadiazine-sensitive individuals. Azithromycin is used in combination with atovaquone for treatment of babesiosis and cytauxzoonosis.

Paromomycin

Paromomycin is the only aminoglycoside antibiotic that has efficacy against protozoa. It is poorly absorbed from the gastrointestinal tract and so has been used to treat enteric protozoal infections, particularly cryptosporidiosis. It is ineffective for treatment of trichomoniasis in cats. Furthermore, when used to treat

intestinal protozoal infections in cats, paromomycin has been absorbed systemically because of intestinal mucosal compromise, with resultant acute renal failure, deafness, and cataract formation. As a result, its use has been limited. In human patients, paromomycin has been used topically to treat cutaneous leishmaniasis and parenterally to treat visceral leishmaniasis.

Tetracyclines And Ciprofloxacin

Doxycycline has primarily been used for malaria prophylaxis in humans. Ciprofloxacin is thought to inhibit DNA gyrase within a chloroplast organelle (the apicoplast) of apicomplexan parasites. It is an alternative to sulfadiazine for treatment of isosporiasis in human patients. Tetracyclines and ciprofloxacin have not been widely used for prevention or treatment of protozoal infections in dogs and cats with the possible exception of doxycycline as part of combination treatment for babesiosis.

Antiprotozoal Drugs Used for Systemic Protozoal Infections

- **Quinolone Derivatives**

Atovaquone

Atovaquone is a hydroxynaphthoquinone that inhibits electron transport in protozoa by targeting the cytochrome bc₁ complex. It has been used in combination with other antiprotozoal drugs as an alternative treatment for malaria, toxoplasmosis, and pneumocystosis in human patients.¹⁸ In veterinary medicine, atovaquone is used in combination with azithromycin for treatment of *Babesia gibsoni* and *Babesia conradae* infections and cytauxzoonosis, but is expensive. Resistance has been reported in *Plasmodium spp.*, *T. gondii*, *Pneumocystis jirovecii*, and canine *B. gibsoni* strains as a result of mutations in the cytochrome bc₁ complex.

Suggested Doses of Drugs Primarily Used to Treat Systemic Protozoal Diseases Excluding Leishmaniasis and Trypanosomiasis in Small Animals

Drug	Dose (mg/kg)	Interval (hours)	Species	Route	Duration (days)	Comments
Pyrimethamine	1 0.5-1	24	D C	PO	14-28	Primarily neosporosis, toxoplasmosis, and American hepatozoonosis. Use with a sulfonamide. Use caution with hepatic and renal insufficiency. Monitor CBC. Folinic acid supplementation (5 mg/day) may be required.
Clindamycin	22	12	D, C	PO		Toxoplasmosis, neosporosis, sarcocystosis, and American hepatozoonosis.
Azithromycin	10	24	D, C	PO	10	Babesiosis and cytauxzoonosis. Used with atovaquone.
Atovaquone	13.3 15	8	D C	PO	10	Babesiosis and cytauxzoonosis with azithromycin. Administer with food.
Decoquinatate	10-20	12	D	PO	≥365	American hepatozoonosis and sarcocystosis. Powder (6% decoquinatate; 60 mg active ingredient per gram) is mixed with food. This equates to 0.5 to 1 table-spoon/10 kg body weight q12h.
Imidocarb dipropionate	6.6 5	Once, repeat in 14 days	D C	Deep IM	N/A	Large <i>Babesia</i> spp. infections. Caution with hepatic or renal insufficiency. Avoid use with other cholinesterase inhibitors.
Diminazene aceturate	3-5	Once	D	Deep IM	N/A	Babesiosis and African trypanosomiasis. Narrow therapeutic range.
Ponazuril	20-50	12-24	D	PO	3-28	Toxoplasmosis, neosporosis, isosporiasis. Optimal dose, duration, efficacy, and adverse effects unknown.
Toltrazuril	5-10 18	12-24	D C	PO	1-14	Hepatozoonosis, isosporiasis. One dose may be effective for isosporiasis. Optimal dose and duration for hepatozoonosis unknown.