71 CHAPTER 71 Antiprotozoal Chemotherapy

Craig E. Greene

Sidney A. Ewing

Table 71-1 summarizes the indications for current antiprotozoal drugs. See Chapters 72 to 82 for details about chemotherapy for specific diseases. Dosages of various drugs are available in the Drug Formulary, Appendix 8.

71.1 AZO-NAPHTHALENE DRUGS

Trypan blue was one of the first compounds used to treat babesiosis. Because local irritation and abscesses develop after subcutaneous (SC) injection, it is administered intravenously (IV). Trypan blue does not completely eliminate *Babesia* organisms, but infected animals recover from illness and remain in a state of premunition. They must be treated with aromatic diamidines (see Aromatic Diamindines) within 1 month to be cured. A disadvantage of trypan blue is that it stains all body tissues and secretions for several weeks.

71.2 ACRIDINE DYES

Quinacrine, developed as a human antimalarial drug, has been administered to dogs as an alternative treatment to nitroimidazoles for giardiasis. It becomes incorporated into the DNA of the organism and inhibits nucleic acid synthesis. Evidence of toxicity includes vomiting, fever, pruritus, neurologic signs, yellow discoloration of urine and tissues, and hepatic dysfunction. It is no longer available in the United States.

71.3 QUINOLINE AND QUINOLONE DERIVATIVES

Diiodohydroxyquin and iodochlorhydroxyquin are halogenated oxyquinolines that have been provided as topical antifungal drugs. They are also amebicidal when administered orally. They are not absorbed systemically and have relatively low toxicity. Signs of toxicity are abdominal pain, diarrhea, and neurologic signs, all of which have been reported in dogs. Atovaquone is a closely related hydroxynaphthoquinone derivative licensed to treat *Pneumocystis* species infections. It has been used in combination with azithromycin to treat babesiosis in people and dogs (see Chapter 77).[44] Buparvaquone, which has been used to treat theileriosis in herbivores, has not effectively treated leishmaniasis or cytauxzoonosis in dogs or cats, respectively.[96] Decoquinate, an hydroxyquinolone licensed for treating coccidiosis in poultry, is effective in ameliorating the signs of hepatozoonosis (see Chapter 74 and Drug Formulary, Appendix 8).[54]

71.4 AROMATIC DIAMIDINES

Phenamidine, pentamidine, diminazene, amicarbalide, and imidocarb, which are diamidine derivatives, are the drugs of choice for treating *Babesia, Cytauxzoon,* and African *Trypanosoma* species infections in dogs and cats. They also effectively treat some other protozoa (see Table 71-1) by interfering with nucleic acid metabolism. These drugs are formulated as salts to reduce irritation after parenteral (intramuscular or SC) injection. Pentamidine has also been used to treat leishmaniasis.[77]

Diamidines are rapidly effective and usually resolve clinical signs and parasitemia within 24 hours. They do not completely eradicate the organisms but have residual activity after a single injection. The drugs become highly

concentrated in parenchymal organs such as the liver and brain and are slowly metabolized or excreted unchanged. The slow metabolism and elimination of diamidines contribute to their prophylactic effects for many weeks after a single injection. Subtherapeutic dosages may allow organisms to develop resistance to these drugs.

71.5 NITROIMIDAZOLES

Nitroimidazoles are effective against anaerobic enteric protozoa that cause trichomoniasis, amebiasis, giardiasis, and balantidiasis. They can be used to treat intraintestinal and invasive parasites. The nitrogroup within anaerobic protozoa and bacteria undergoes a reduction to produce various unstable metabolites, some of which have antimicrobial activity. The drugs are generally much less effective against microaerophilic or aerobic microorganisms. Metronidazole, tinidazole, nimorazole, dimetridazole, secnidazole, and ornidazole are close structural analogs marketed in various regions of the world. Metronidazole is the most widely used of these compounds. In addition to protozoa, it is active against obligate spore-forming anaerobes such as *Clostridium*, some non–spore-forming anaerobes such as *Campylobacter*, and microaerophilic organisms such as species belonging to the Enterobacteriaceae. Metronidazole is generally preferred for treating giardiasis.[83] *Giardia* infections that are resistant to metronidazole have been effectively treated by combining treatment with quinacrine.[66] Metronidazole is the drug of choice for treating invasive amebiasis in people.

Table 71-1 Properties of Antiprotozoal Drugs

GENERIC NAME (TRADE NAME)[a]	INFECTIONS INDICATED: FIRST CHOICE	INFECTIONS INDICATED: ALTERNATE CHOICE
Azo-Naphthalene Dyes		
Trypan blue	None	*Babesia*
Acridine Dyes		
Quinacrine hydrochloride (Atabrine, Keybrin)	None	*Giardia*
Quinoline and Quinolone Derivatives		
Diiodohydroxyquin (iodoquinol; Diodoquin, Yodoxin)	*Balantidium*	*Entamoeba*
Iodochlorhydroxyquin (clioquinol; Vioform)	*Balantidium*	*Entamoeba*
Decoquinate (Deccox)	*Hepatozoon*	Coccidiosis
Hydroxynaphthoquinones		
Atovaquone (Mepron)	None	*Babesia*, *Pneumocystis*, Toxoplasma
Aromatic Diamidines		
Pentamidine isethionate (Lomidine, Pentam, NebuPent); also phenamidine	*Babesia, Acanthamoeba*	*Leishmania*, *Pneumocystis*
Diminazene aceturate (Berenil, Ganaseg)	*Cytauxzoon, Babesia,* African *Trypansoma*	*Hepatozoon canis*
Imidocarb dipropionate (Imizol)	*Babesia, Hepatozoon canis, Cytauxzoon*	*Ehrlichia*
Amicarbalide (Diampiron)	*Ehrlichia*	None
Nitroimidazoles		
Metronidazole (Flagyl, Stomorgyl[b])	*Giardia*, *Pentatrichomonas*	*Entamoeba* (invasive), *Balantidium*
Dimetridazole (Emtryl)	*Entamoeba, Balantidium*	None
Tinidazole (Fasigyn)	*Pentatrichomonas*	*Babesia, Giardia*
Benzimidazoles		
Fenbendazole (Panacur)	Helminths, *Giardia*	None
Albendazole (Valbazan)	*Giardia*, *Encephalitozoon*	None
Febantel-Praziquantel-Pyrantel pamoate (Drontal-plus)	Helminths	*Giardia*
Ionophores		
Monensin (Rumensin, Coban)	Coccidia	*Toxoplasma*
Lasalocid (Bovatec)	Coccidia	None
Salinomycin (Bio-cox)	Coccidia	None
Antimonials		
Sodium stibogluconate (Pentostam)	*Leishmania*	None
Meglumine antimoniate (Glucantime)	*Leishmania*	None
Antibacterials		
Paromomycin (Humatin, Aminosidine)	*Cryptosporidium, Pentatrichomonas*	*Entamoeba*, *Giardia, Leishmania*
Furazolidone (Furoxone)	Coccidia	*Giardia*
Nifurtimox (Lampit)	*Trypanosoma cruzi*	*Leishmania*
Tetracycline, doxycycline (many formulations)	*Balantidium*	*Hepatozoon canis*
Trimethoprim-sulfonamide (Tribrissen, Ditrim, Bactrim, Septra)	*Pneumocystis,* Coccidia, *Cyclospora, Neospora*	*Acanthamoeba*
Pyrimethamine (Daraprim)	*Toxoplasma*, *Neospora*	*Pneumocystis*
Spiramycin (Rovamycin, Stomorgyl[b])	*Cryptosporidium*	*Toxoplasma*
Clindamycin (Antirobe, Cleocin)	*Toxoplasma*, *Neospora*	*Babesia*
Azithromycin (Zithromax)	*Toxoplasma*	*Babesia*, *Cryptosporidium*

Miscellaneous		
Bismuth-*N*-glycolylarsanilate (Milibis-V)	None	*Entamoeba, Giardia*
Amprolium (Amprol, Corid)	None	Coccidia
Amphotericin B (Fungizone, Albecet[c])	*Acanthamoeba*	*Leishmania*
Phosphocholine (Oleyl-Pc, Miltefosine)	*Leishmania*	*Trypanosoma*
Toltrazuril (Baycox)	Coccidia	*Toxoplasma, Hepatozoon*
Ponazuril (Marquis)	*Neospora*	*Sarcocystis*
Ketoconazole (Nizoral)	*Leishmania*	None
Allopurinol (Zyloprim[d])	*Leishmania*	*Trypanosoma cruzi*
Fumagillin	*Encephalitozoon*	*Entamoeba*
Suramin (Metaret)	African *Trypanosoma*	Feline leukemia virus
Interferon-γ[d]	*Leishmania*	None

a See Drug Formulary, Appendix 8, for additional information on these drugs.

b Combination of metronidazole (25, 125, 250 mg) with spiramycin (46.9, 234, 469 mg) in tablets.

c Lipid formulations preferred.

d Used in combination with antimonials for leishmaniasis.

Metronidazole is almost completely absorbed after oral administration. Food does not reduce the extent of absorption but may delay the rate. IV administration of metronidazole may be preferable in severely ill patients but is expensive and potentially more neurotoxic. The drug distributes widely and penetrates body tissues, extracellular fluids, and even pus-filled cavities. Metronidazole achieves good concentrations in the central nervous system (CNS) even in the absence of inflammation. It is extensively metabolized in the liver, but renal excretion of active drug also occurs.

Metronidazole has been administered alone and with spiramycin to treat periodontal disease and stomatitis and in combination with aminoglycosides to treat mixed infections associated with bowel perforation and intraabdominal sepsis (see Chapter 89). In people the drug effectively treats intraabdominal, pelvic, pleuropulmonary, CNS, and bone and joint infections.

Side effects of metronidazole include gastrointestinal irritation with signs of vomiting and anorexia, glossitis, and stomatitis. Neurologic signs may be seen in dogs and cats after 7 to 10 days of treatment with high dosages (greater than 66 mg/kg/day) and may be resolved when therapy is discontinued.[12] Some dogs have developed fatal encephalopathy, persistent seizures, or cerebellar and central vestibular ataxia after therapy; diazepam helped the dogs recover (see Drug Formulary, Appendix 8).[20]

71.6 BENZIMIDAZOLES

Fenbendazole and albendazole are broad-spectrum benzimidazoles that are used to treat a wide range of infections with helminths and selected protozoa. They affect microtubule synthesis in the protozoal cytoskeleton. Both drugs have been effective in the treatment of intestinal giardiasis and are often more potent than metronidazole.[30] Fenbendazole is relatively safe, and dosages used for treating helminths (50 mg/kg for 3 days) are effective in treating giardiasis.[30,82,100] The drug was not as effective in cats that were coinfected with *Cryptosporidium*.[41] Fenbendazole use was associated with development of granulocytopenia as an idiosyncratic reaction in one dog.[23a] Myelotoxicity has been caused by albendazole use in dogs and cats[89] but can be reversed after treatment is discontinued. Febantel, which is metabolized to fenbendazole, is one component of an antihelmentic combination that is effective against *Giardia*.[6,70]

71.7 AZOLES

The antifungal drugs ketoconazole, fluconazole, and terbinafine have some antileishmanial activity, because the infecting organism has ergosterol in its cell wall. In experimental animal models, these drugs have been less effective than other antiprotozoal drugs. Another antifungal, amphotericin B (AMB), has been more effective (see below, Miscellaneous drugs).

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71.8 IONOPHORES

Ionophores are compounds that form lipid-soluble complexes with cations, which facilitate transport of the ions across biologic membranes. They are antibiotics isolated from *Streptomyces* spp. and are provided primarily as coccidiostats. Monensin, lasalocid, and salinomycin, the compounds used in veterinary medicine, cause accumulation of intracellular ions within the parasite, interfering with its metabolism. They have been used primarily as growth promoters in food animal practice, although monensin has been effective in reducing shedding of *Toxoplasma* oocysts by cats. The ionophores also have antibacterial activity and have been used experimentally to treat endotoxic shock in dogs. Because of their stimulatory effects on cardiac contractility and myocardial perfusion, their toxicity may be increased by concurrent administration of cardiac glycosides.

71.9 ANTIMONIALS

Sodium stibogluconate and meglumine antimoniate are pentavalent antimony compounds and two of the main agents used in the treatment of leishmaniasis.[27,84,91-93] The dosage is based on the amount of antimony compound administered. Treatment with these drugs is not curative, and two or three courses may be necessary. Side effects include anorexia, vomiting, nausea, myalgia, and lethargy. Electrocardiogram abnormalities and nephrotoxicity can develop at higher dosages. Although these antimonials are often given parenterally, a cyclodextrin formulation was found to have good bioavailability in mice.[16]

71.10 ANTIBACTERIALS

Paromomycin (aminosidine) and furazolidone are nonabsorbable antibacterials (previously discussed; see Chapter 34). They are effective in treating some intestinal protozoal infections. Because of potential intestinal absorption and nephrotoxicity, paromomycin—an aminoglycoside—must be administered with caution when treating amebiasis or trichomoniasis when bowel lesions are extensive. Paromomycin has also been used to treat leishmaniasis. Furazolidone and sulfonamides are effective in treating intestinal coccidial infections. Nifurtimox, a nitrofuran derivative, can suppress but not cure *Trypanosoma cruzi* infections. Nausea, vomiting, and convulsions may be side effects.

Trimethoprim, an antibacterial diaminopyrimidine compound that inhibits folic acid synthesis, has broad-spectrum antimicrobial activity (see Chapter 34). Combined with sulfonamides, it has been used to treat *Pneumocystis* and coccidial infections. Pyrimethamine is closely related to trimethoprim but is more effective against protozoa. It has been used in combination with sulfonamides to treat infections with *Neospora* and *Toxoplasma* organisms.

Several newer antifolate drugs (see Chapter 80) under development may also be active against these two protozoa. Clindamycin, a lincosamide antimicrobial drug, and certain macrolides (azithromycin, clarithromycin) are also active against these two protozoa.

Spiramycin, a macrolide antibiotic, has an antibacterial spectrum similar to that of erythromycin but is less effective. Absorption after oral administration is adequate for therapeutic purposes. It is widely distributed and reaches high concentrations in tissues, from which it is slowly eliminated in the bile and urine. Its usefulness has been limited for treating bacterial infections in veterinary medicine, but it is now marketed in combination with metronidazole, primarily to treat periodontal and oral infections. Spiramycin has been found to be somewhat effective for treating intestinal cryptospori-diosis and has been given to people to treat acute toxoplasmosis.

71.11 MISCELLANEOUS DRUGS

Bismuth-*N*-glycoloylarsanilate is an antihelmintic drug that is a second choice for treating giardiasis. Amprolium is a thiamine inhibitor that is commonly chosen to treat coccidiosis in dogs, although it is not approved by the Food and Drug Administration for this purpose (see Chapter 81). Overdoses may produce neurologic signs. As mentioned previously, the antifungal drug AMB is effective in treating leishmaniasis because the infecting protozoa have ergosterol in their cell walls. It is much more efficient than other drugs in treating human patients.[61] Lipid emulsions may improve this efficacy and lower toxicity.[15] Toltrazuril is an anticoccidial agent that is unrelated to the others. It appears to be very effective in eliminating coccidia in most animals without interfering with a persistent host immune response.[25,26] Toltrazuril has been used to control oocyst shedding by cats acutely infected with *Toxoplasma* organisms.[52] The drug can be given by mouth in water or food, systemically by SC injection, or by topical application. A sulfone derivative of the drug (ponazuril) is effective in treating *Sarcocystis neurona* infection in horses,[22] and it has been used to treat *Neospora caninum* infection in calves and dogs[45] (see Drug Formulary, Appendix 8). Nitazoxanide is a thiazolide compound that has been approved for use in people with drug-resistant *Giardia* and *Cryptosporidium* infections. Allopurinol is a pyrazolopyrimidine that interferes with nucleic acid synthesis in *Leishmania* and *T. cruzi* organisms. It has been licensed to treat hyperuricemia and gout in people but is now being used to treat American trypanosomiasis and leishmaniasis in endemic areas (see Chapters 72 and 73).[*] Miltefosine (hexadecylphosphocholine) is a membrane active drug that accumulates in macrophages and is active against *Leishmania* while simultaneously stimulating T-cell activation and production of toxic intracellular intermediates. Although the orally administered drug has been effective in treating *Leishmania*-infected people,[75,90] side effects are more severe in dogs, so other derivatives of phosphocholine are recommended (see Drug Formulary, Appendix 8). Antihelmintics containing febantel have been used to treat dogs with giardiasis.[70]

* References 17, 24, 35, 43, 48, 51, 55, 95.

71.12 Suggested Readings[†]

† See the CD-ROM for a complete list of references.

6. Barr, SC, Bowman, DD, Frongillo, MF, et al.: Efficacy of a drug combination of praziquantel, pyrantel pamoate, and febantel against giardiasis in dogs. *Am J Vet Res*. **59**, 1998, 1134–1136. 675

17. Denerolle, P, Bourdoiseau, G: Combination allopurinol and antimony treatment versus antimony alone and allopurinol alone in the treatment of canine leishmaniasis (96 cases). *J Vet Intern Med*. **13**, 1999, 413–415. 676

45. Kritzner, S, Sager, H, Blum, J, et al.: An explorative study to assess the efficacy of toltrazuril-sulfone (Ponazuril) in calves experimentally infected with *Neospora caninum*. *Ann Clin Microbiol Antimicrob*. **1**, 2002, 4.

70. Payne, PA, Ridley, RK, Dryden, MW, et al.: Efficacy of a combination febantel-praziquantel-pyrantel product, with or without vaccination with a commercial *Giardia* vaccine, for treatment of dogs with naturally occurring giardiasis. *J Am Vet Med Assoc*. **220**, 2002, 330–333.

95. Vercammen, F, Fernandez-Perez, FJ, del Amo, C, et al.: Follow-up of *Leishmania infantum* naturally infected dogs treated with allopurinol: immunofluorescence antibody test, ELISA and Western blot. *Acta Trop*. **84**, 2002, 175–181.

71.13 Uncited references

1. Abboud, P, Lemee, V, Gargala, G, et al.: Successful treatment of metronidazole- and albendazole-resistant giardiasis with nitazoxanide in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis.* **32**, 2001, 1792–1794.

5. Baneth, G, Shaw, S: Chemotherapy of canine leishmaniasis. *Vet Parasitol*. **106**, 2002, 315–324.

11. Cavaliero, T, Arnold, P, Mathis, A, et al.: Clinical serologic and parasitologic follow-up after long-term allopurinol therapy of dogs naturally infected with *Leishmania infantum*. *J Vet Intern Med.* **13**, 1999, 330–334.

29. Greene, CE, Latimer, K, Hopper, E, et al.: Administration of diminazene aceturate or imidocarb dipropionate for treatment of cytauxzoonosis in cats. *J Am Vet Med Assoc*. **215**, 1999, 497–500.

41. Keith, CL, Radecki, SV, Lappin, MR: Evaluation of fenbendazole for treatment of *Giardia* infection in cats concurrently infected with *Cryptosporidium parvum*. *Am J Vet Res*. **64**, 2003, 1027–1029.

78. Riera, C, Valladares, JE, Gallego, M, et al.: Serological and parasitological follow-up in dogs experimentally infected with *Leishmania infantum* and treated with meglumine antimoniate. *Vet Parasitol*. **84**, 1999, 33–47.

79. Sánchez, S, Sallovitz, J, Savio, E, et al.: Comparative availability of two oral dosage forms of albendazole in dogs. *Vet J*. **160**, 2000, 153–156.