Antiprotozoal Drugs

**I. OVERVIEW**

Protozoal infections are common among people in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases, such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis, are no longer confined to specific geographic locales. Because they are eukaryotes, the unicellular protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity, such as neuronal, renal tubular, intestinal, and bone marrow stem cells. Most antiprotozoal agents have not proved to be safe for pregnant patients. Drugs used to treat protozoal infections are summarized in Figure 36.1.

**II. CHEMOTHERAPY FOR AMEBIASIS**

Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. The disease can be acute or chronic, with patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. The diagnosis is established by isolating E. histolytica from fresh feces. Therapy is aimed not only at the acutely ill patient but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others.

1. **Life cycle of Entamoeba histolytica**

Entamoeba histolytica exists in two forms: cysts that can survive out- side the body and labile but invasive trophozoites that do not persist outside the body. Cysts, ingested through feces-contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated. The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine or simply feed on intestinal bacteria. [Note: One strategy for treating luminal amebiasis is to add antibiotics, such as tetracycline, to the treatment regimen, resulting in a reduction in intestinal flora, the ameba’s major food source.] The trophozoites within the intestine are slowly carried toward the rec- tum, where they return to the cyst form and are excreted in feces. Large numbers of trophozoites within the colon wall can also lead to systemic invasion. A summary of the life cycle of E. histolytica is pre- sented in Figure 36.2.

1. **Classification of amebicidal drugs**

Therapeutic agents are classified as luminal, systemic, or mixed (luminal and systemic) amebicides according to the site where the drug is effective (see Figure 36.2). For example, luminal amebicides act on the para- site in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed amebicides are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

**C. Mixed amebicides (metronidazole and tinidazole**)

**1. Metronidazole**: Metronidazole [me-troe-NYE-da-zole], a nitroimida- zole, is the mixed amebicide of choice for treating amebic infections and kills the E. histolytica trophozoites. [Note: Metronidazole also finds extensive use in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, and anaerobic gram- negative bacilli (for example, Bacteroides species). Metronidazole is the drug of choice for the treatment of pseudomembranous colitis caused by the anaerobic, gram-positive bacillus Clostridium diffi cile and is also eff ective in the treatment of brain abscesses caused by these organisms.]

**a. Mechanism of action**: Some anaerobic protozoal parasites (including amebas) possess ferrodoxin-like, low-redox-potential, electron-transport proteins that participate in metabolic electron removal reactions. The nitro group of metronidazole is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.

**b. Pharmacokinetics**: Metronidazole is completely and rapidly absorbed after oral administration (Figure 36.3). [Note: For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as iodoquinol or paromomycin. This combination provides cure rates of greater than 90 percent.] Metronidazole distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF). Metabolism of the drug depends on hepatic oxidation of the metronidazole side chain by mixed-function oxidase, followed by glucuronylation. Therefore, concomitant treatment with inducers of this enzymatic system, such as phenobarbital, enhances the rate of metabolism. Conversely, those drugs that inhibit this system, such as cimetidine, prolong the plasma half-life of metronidazole. The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine.

**c. Adverse effects**: The most common adverse effects are those associated with the gastrointestinal tract, including nausea, vomiting, epigastric distress, and abdominal cramps (Figure 36.4). An unpleasant, metallic taste is commonly experienced. Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicologic problems, such as dizziness, vertigo, and numbness or paresthesias in the peripheral nervous system. [Note: The latter are reasons for discontinuing the drug.] If taken with alcohol, a disulfiram-like effect occurs (see p. 120 ).

**d. Resistance**: Resistance to metronidazole is not a therapeutic problem, although strains of trichomonads resistant to the drug have been reported.

**2. Tinidazole**: Tinidazole [tye-NI-da-zole] is a second-generation nitro- imidazole that is similar to metronidazole in spectrum of activity, absorption, adverse effects, and drug interactions. It was approved by the U.S. Food and Drug Administration in 2004 for treatment of amebiasis, amebic liver abcess, giardiasis, and trichomoniasis but was used outside the United States for decades prior to approval. Tinidazole is as eff ective as metronidazole, with a shorter course of treatment, yet is more expensive than generic metronidazole.

**D. Luminal amebicides**

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as iodoquinol, diloxanide furoate, or paromomycin, should be administered for treatment of the asymptomatic colonization state.

**1. Iodoquinol**: Iodoquinol [eye-oh-doe-QUIN-ole], a halogenated 8-hydroxy quinolone, is amebicidal against E. histolytica and is effective against the luminal trophozoite and cyst forms. Side effects from iodoquinol include rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

**2. Paromomycin**: Paromomycin [par-oh-moe-MYE-sin], an aminogly- coside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, because it is not significantly absorbed from the gastrointestinal tract. It is an alternative agent for cryptosporidiosis. Paramomycin is directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora. Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage. Very little of the drug is absorbed on oral ingestion, but that which is absorbed is excreted in urine. Gastrointestinal distress and diarrhea are the principal adverse effects.

**E. Systemic amebicides** These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas.

**1. Chloroquine**: Chloroquine [KLOR-oh-kwin] is used in combination with metronidazole and diloxanide furoate to treat and prevent amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Chloroquine is also effective in the treatment of malaria.

**2. Emetine and dehydroemetine**: Emetine [EM-e-teen] and dehydroemetine [de-hye-dro-EM-e-teen] are alternative agents for the treatment of amebiasis. They inhibit protein synthesis by blocking chain elongation.1 Intramuscular injection is the preferred route. Emetine is concentrated in the liver, where it persists for a month after a single dose. It is slowly metabolized and excreted, and it can accumulate. Its half-life in plasma is 5 days. The use of these ipecac alkaloids is limited by their toxicities (dehydroemetine is less toxic than emetine), and close clinical observation is necessary when these drugs are administered. They should not be taken for more than 5 days. Dehydroemetine is only available under a compassionate inves- tigational new drug protocol through the Centers of Disease Control and Prevention. Among the untoward effects are pain at the site of injection, transient nausea, cardiotoxicity (for example, arrhythmias and congestive heart failure), neuromuscular weakness, dizziness, and rashes. A summary of the treatment of amebiasis is shown in Figure 36.5.

**III. CHEMOTHERAPY FOR MALARIA**

Malaria is an acute infectious disease caused by four species of the pro- tozoal genus Plasmodium. The parasite is transmitted to humans through the bite of a female Anopheles mosquito, which thrives in humid, swampy areas. Plasmodium falciparum is the most dangerous species, causing an acute, rapidly fulminating disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs). P. falciparum infection can lead to capillary obstruction and death if treatment is not instituted promptly. Plasmodium vivax causes a milder form of the disease. Plasmodium malariae is common to many tropical regions, but Plasmodium ovale is rarely encountered. Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment of P. falciparum.

1. **Life cycle of the malarial parasite**

When an infected mosquito bites, it injects Plasmodium sporozoites into the bloodstream (Figure 36.6). The sporozoites migrate through the blood to the liver, where they form cyst-like structures containing thousands of merozoites. [Note: Diagnosis depends on laboratory identification of the parasites in red blood cells of peripheral blood smears.] Upon release, each merozoite invades a red blood cell, becoming a trophozoite and using hemoglobin as a nutrient. The trophozoites mul- tiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. [Note: Alternatively, released merozoites can become gametocytes, which are picked up by mosquitoes from the blood they ingest. The cycle thus begins again, with the gametocytes becoming sporozoites in the insect.] The eff ectiveness of drug treatment is related to the par- ticular species of infecting plasmodium and the stage of its life cycle that is targeted. A summary of the life cycle of the parasite and the sites of therapeutic interventions are presented in Figure 36.6.

1. **Tissue schizonticide: Primaquine**

Primaquine [PRIM-a-kwin] is an 8-aminoquinoline that eradicates prima- ry exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale). [Note: Primaquine is the only agent that can lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver in the exoerythro- cytic form after the erythrocytic form of the disease is eliminated.] The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease. [Note: Primaquine is not eff ec- tive against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as chloroquine, quinine, mefl oquine, or pyrimethamine.]

 **1. Mechanism of action**: This is not completely understood. Metabolites of primaquine are believed to act as oxidants that are responsible for the schizonticidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities.

**2. Pharmacokinetics**: Primaquine is well absorbed on oral administra- tion and is not concentrated in tissues. It is rapidly oxidized to many compounds, primarily the deaminated drug. Which compound possesses the schizontocidal activity has not been established. Metabolites appear in urine (Figure 36.7).

**3. Adverse effects**: Primaquine has a low incidence of adverse effects, except for drug-induced hemolytic anemia in patients with genetically low levels of glucose-6-phosphate dehydrogenase2 (Figure 36.8). Other toxic manifestations observed after large doses of the drug include abdominal discomfort, especially when administered in combination with chloroquine (which may aff ect patient com- pliance), and occasional methemoglobinemia. Granulocytopenia and agranulocytosis are rarely seen, except in patients with lupus or arthritis, because both conditions are aggravated by the drug. Primaquine is contraindicated during pregnancy. All Plasmodium species may develop resistance to primaquine.

**C. Blood schizonticide**: **Chloroquine**

Chloroquine [KLOR-oh-kwin] is a synthetic 4-aminoquinoline that has been the mainstay of antimalarial therapy, and it is the drug of choice in the treatment of erythrocytic P. falciparum malaria, except in resistant strains. Chloroquine is less effective against P. vivax malaria. It is highly specifi c for the asexual form of plasmodia. Chloroquine is also effective in the treatment of extraintestinal amebiasis. [Note: The anti- inflammatory action of chloroquine explains its occasional use in rheu- matoid arthritis and discoid lupus erythematosus.]

**1. Mechanism of action**: Although a detailed explanation of the mechanisms by which chloroquine kills plasmodial parasites is still incomplete, the following processes are essential for the drug’s lethal action (Figure 36.9). After traversing the erythrocytic and plasmodial membranes, chloroquine (a diprotic weak base) is concentrated in the organism’s acidic food vacuole, primarily by ion trapping. It is in the food vacuole that the parasite digests the host cell’s hemo- globin to obtain essential amino acids. However, this process also releases large amounts of soluble heme (ferriprotoporphyrin IX), which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozoin (a pigment), which is sequestered in the parasite’s food vacuole. Chloroquine specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cell. The binding to heme and prevention of its polymeriza- tion appear to be a crucial step in the drug’s antiplasmodial activity, which may represent a unifying mechanism for such diverse compounds as chloroquine, quinidine, and mefloquine.

**2. Pharmacokinetics**: Chloroquine is rapidly and completely absorbed following oral administration. Usually, 4 days of therapy suffice to cure the disease. The drug has a very large volume of distribution and concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes. It persists in erythrocytes (see “Mechanism of action” above). The drug also penetrates the central nervous system (CNS) and traverses the placenta. Chloroquine is dealkylated by the hepatic mixed-function oxidase system, but some metabolic products retain antimalarial activity. Both parent drug and metabolites are excreted predominantly in urine (Figure 36.10). The excretion rate is enhanced with acidified urine.

**3. Adverse effects**: Side effects are minimal at the low doses used in the chemosuppression of malaria. At higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurred vision (Figure 36.11). [Note: An ophthalmologic examination should be routinely performed.] Discoloration of the nail beds and mucous membranes may be seen on chronic administration. Chloroquine should be used cautiously in patients with hepatic dysfunction or severe gastrointestinal problems and in patients with neurologic or blood disorders. Chloroquine can cause electrocardio- graphic (ECG) changes, because it has a quinidine-like eff ect. It may also exacerbate dermatitis produced by gold or phenylbutazone ther- apy. [Note: Patients with psoriasis or porphyria should not be treated with chloroquine, because an acute attack may be provoked.]

**4. Resistance**: Resistance of plasmodia to available drugs has become a serious medical problem throughout Africa, Asia, and most areas of Central and South America. Chloroquine-resistant P. falciparum exhibit multigenic alterations that confer a high level of resistance. [Note: When a chloroquine-resistant organism is encountered, ther- apy usually consists of an orally administered combination of qui- nine, pyrimethamine, and a sulfonamide such as sulfadoxine.]

**D. Blood schizonticide**: **Mefl oquine**

Mefl oquine [MEF-lo-kween] appears to be promising as an effective single agent for suppressing and curing infections caused by multidrug- resistant forms of P. falciparum. Its exact mechanism of action remains to be determined, but, like quinine, it can apparently damage the para- site’s membrane. Resistant strains have been identifi ed. Mefloquine is absorbed well after oral administration and concentrates in the liver and lung. It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems. The drug undergoes extensive metabolism. Its major excretory route is through the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. ECG abnormalities and cardiac arrest are possible if mefl oquine is taken concurrently with qui- nine or quinidine.

**E. Blood schizonticides: Quinine**

Quinine [KWYE-nine] interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. It is reserved for severe infestations and for malarial strains that are resistant to oth-er agents such as chloroquine. Taken orally, quinine is well distributed throughout the body and can reach the fetus in pregnant patients. Alkalinization of urine decreases its excretion. The major adverse effect of quinine is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not considered to be reasons for suspending therapy. However, quinine treatment should be suspended if a positive Coombs test for hemolytic anemia occurs. Drug interactions include potentiation of neuromuscular-blocking agents and elevation of digoxin levels if taken concurrently with qui- nine. Quinine absorption is retarded when the drug is taken with alumi- num-containing antacids. Quinine is fetotoxic.

**F. Blood schizonticide**: **Artemisinin**

 Artemisinin [ar-te-MIS-in-in] is derived from the qinghaosu plant, which has been used in Chinese medicine for more than 2 millennia in the treatment of fevers and malaria. Artemisinin (or one of its derivatives) is available for the treatment of severe, multidrug-resistant P. falciparum malaria. Its antimalarial action involves the production of free radicals within the plasmodium food vacuole, following cleavage of the drug’s endoperoxide bridge by hemeiron in parasitized erythrocytes. It is also believed to covalently bind to and damage specific malarial proteins. Oral, rectal, and intravenous (IV) preparations are available, but the short