

meal, and is dose-limited above 750 mg. The elimination half-life is increased in patients with moderate hepatic impairment. Because of the potential for drug accumulation, the use of atovaquone is generally contraindicated in persons with a creatinine clearance rate <30 mL/min. No dosage adjustments are needed in patients with mild to moderate renal impairment.

**Azithromycin** See Table 246e-1 and Chap. 170.

**Azoles** See Table 246e-1 and Chap. 235.

**Benznidazole\*** This oral nitroimidazole derivative is used to treat Chagas' disease, with cure rates of 80–90% recorded in acute infections. Benznidazole is believed to exert its trypanocidal effects by generating oxygen radicals to which the parasites are more sensitive than mammalian cells because of a relative deficiency in antioxidant enzymes. Benznidazole also appears to alter the balance between pro- and anti-inflammatory mediators by downregulating the synthesis of nitrite, interleukin (IL) 6, and IL-10 in macrophages. Benznidazole is highly lipophilic and readily absorbed. The drug is extensively metabolized; only 5% of the dose is excreted unchanged in the urine. Benznidazole is well tolerated; adverse effects are rare and usually manifest as GI upset or pruritic rash.

**Chloroquine** This 4-aminoquinoline has marked, rapid schizonticidal and gametocidal activity against blood forms of *P. ovale* and *Plasmodium malariae* and against susceptible strains of *P. vivax* and *P. falciparum*. It is not active against intrahepatic forms (*P. vivax* and *P. ovale*). Parasitized erythrocytes accumulate chloroquine in significantly greater concentrations than do normal erythrocytes. Chloroquine, a weak base, concentrates in the food vacuoles of intraerythrocytic parasites because of a relative pH gradient between the extracellular space and the acidic food vacuole. Once it enters the acidic food vacuole, chloroquine is rapidly converted to a membrane-impermeable protonated form and is trapped. Continued accumulation of chloroquine in the parasite's acidic food vacuoles results in drug levels that are 600-fold higher at this site than in plasma. The high accumulation of chloroquine results in an increase in pH within the food vacuole to a level above that required for the acid proteases' optimal activity, inhibiting parasite heme polymerase; as a result, the parasite is effectively killed with its own metabolic waste. Compared with susceptible strains, chloroquine-resistant plasmodia transport chloroquine out of intraparasitic compartments more rapidly and maintain lower chloroquine concentrations in their acid vesicles. Hydroxychloroquine, a congener of chloroquine, is equivalent to chloroquine in its antimalarial efficacy but is preferred to chloroquine for the treatment of autoimmune disorders because it produces less ocular toxicity when used in high doses.

Chloroquine is well absorbed. However, because it exhibits extensive tissue binding, a loading dose is required to yield effective plasma concentrations. A therapeutic drug level in plasma is reached 2–3 h after oral administration (the preferred route). Chloroquine can be administered IV, but excessively rapid parenteral administration can result in seizures and death from cardiovascular collapse. The mean half-life of chloroquine is 4 days, but the rate of excretion decreases as plasma levels decline, making once-weekly administration possible for prophylaxis in areas with sensitive strains. About one-half of the parent drug is excreted in urine, but the dose should not be reduced for persons with acute malaria and renal insufficiency.

**Ciprofloxacin** See Table 246e-1 and Chap. 170.

**Clindamycin** See Table 246e-1 and Chap. 170.

**Dapsone** See Table 246e-1 and Chap. 205e.

**Dehydroemetine** Emetine is an alkaloid derived from ipecac; dehydroemetine is synthetically derived from emetine and is considered less toxic. Both agents are active against *Entamoeba histolytica* and appear to work by blocking peptide elongation and thus inhibiting protein synthesis. Emetine is rapidly absorbed after parenteral

administration, rapidly distributed throughout the body, and slowly excreted in the urine in unchanged form. Both agents are contraindicated in patients with renal disease.

**Diethylcarbamazine\*** A derivative of the antihelminthic agent piperazine with a long history of successful use, diethylcarbamazine (DEC) remains the treatment of choice for lymphatic filariasis and loiasis and has also been used for visceral larva migrans. Although piperazine itself has no antifilarial activity, the piperazine ring of DEC is essential for the drug's activity. DEC's mechanism of action remains to be fully defined. Proposed mechanisms include immobilization due to inhibition of parasite cholinergic muscle receptors, disruption of microtubule formation, and alteration of helminthic surface membranes resulting in enhanced killing by the host's immune system. DEC enhances adherence properties of eosinophils. The development of resistance under drug pressure (i.e., a progressive decrease in efficacy when the drug is used widely in human populations) has not been observed, although DEC has variable effects when administered to persons with filariasis. Monthly administration provides effective prophylaxis against both bancroftian filariasis and loiasis.

DEC is well absorbed after oral administration, with peak plasma concentrations reached within 1–2 h. No parenteral form is available. The drug is eliminated largely by renal excretion, with <5% found in feces. If more than one dose is to be administered to an individual with renal dysfunction, the dose should be reduced commensurate with the reduction in creatinine clearance rate. Alkalinization of the urine prevents renal excretion and increases the half-life of DEC. Use in patients with onchocerciasis can precipitate a Mazzotti reaction, with pruritus, fever, and arthralgias. Like other piperazines, DEC is active against *Ascaris* species. Patients co-infected with this nematode may expel live worms after treatment.

**Diloxanide Furoate** Diloxanide furoate, a substituted acetanilide, is a luminally active agent used to eradicate the cysts of *E. histolytica*. After ingestion, diloxanide furoate is hydrolyzed by enzymes in the lumen or mucosa of the intestine, releasing furoic acid and the ester diloxanide; the latter acts directly as an amebicide.

Diloxanide furoate is given alone to asymptomatic cyst passers. For patients with active amebic infections, diloxanide is generally administered in combination with a 5-nitroimidazole such as metronidazole or tinidazole. Diloxanide furoate is rapidly absorbed after oral administration. When coadministered with a 5-nitroimidazole, only diloxanide appears in the systemic circulation; levels peak within 1 h and disappear within 6 h. About 90% of an oral dose is excreted in the urine within 48 h, chiefly as the glucuronide metabolite. Diloxanide furoate is contraindicated in pregnant and breast-feeding women and in children <2 years of age.

**Eflornithine\*** Eflornithine (difluoromethylornithine, or DFMO) is a fluorinated analogue of the amino acid ornithine. Although originally designed as an antineoplastic agent, eflornithine has proven effective against some trypanosomatids. At one point, the production of this effective agent ceased despite the increasing incidence of human African trypanosomiasis; however, production resumed after eflornithine was discovered to be an effective cosmetic depilatory agent.

Eflornithine has specific activity against all stages of infection with *Trypanosoma brucei gambiense*; however, it is inactive against *Trypanosoma brucei rhodesiense*. The drug acts as an irreversible suicide inhibitor of ornithine decarboxylase, the first enzyme in the biosynthesis of the polyamines putrescine and spermidine. Polyamines are essential for the synthesis of trypanothione, an enzyme required for the maintenance of intracellular thiols in the correct redox state and for the removal of reactive oxygen metabolites. However, polyamines are also essential for cell division in eukaryotes, and ornithine decarboxylase is similar in trypanosomes and mammals. The selective antiparasitic activity of eflornithine is partly explained by the structure of the trypanosomal enzyme, which lacks a 36-amino-acid C-terminal sequence found on mammalian ornithine decarboxylase. This difference results in a lower turnover of ornithine decarboxylase and a more rapid decrease of polyamines in trypanosomes than in the mammalian host.