TABLE 248-7 PROPERTIES OF ANTIMALARIAL DRUGS

Drug(s)	Pharmacokinetic Properties	Antimalarial Activity	Minor Toxicity	Major Toxicity
Quinine, quinidine	Good oral and IM absorption (quinine); *Cl* and V_d reduced, but plasma protein binding (principally to ∝1 acid glycoprotein) increased (90%) in malaria; quinine $t_{1/2}$: 16 h in malaria, 11 h in healthy persons; quinidine $t_{1/2}$: 13 h in malaria, 8 h in healthy persons	Acts mainly on trophozoite blood stage; kills gametocytes of *P. vivax*, *P. ovale*, and *P. malariae* (but not *P. falciparum*); no action on liver stages	*Common:* "Cinchonism": tinnitus, high-tone hearing loss, nausea, vomiting, dysphoria, postural hypotension; ECG QT_c interval prolongation (quinine usually by <10% but quinidine by up to 25%) *Rare:* Diarrhea, visual disturbance, rashes *Note:* Very bitter taste	*Common:* Hypoglycemia *Rare:* Hypotension, blindness, deafness, cardiac arrhythmias, thrombocytopenia, hemolysis, hemolytic-uremic syndrome, vasculitis, cholestatic hepatitis, neuromuscular paralysis *Note:* Quinidine more cardiotoxic
Chloroquine	Good oral absorption, very rapid IM and SC absorption; complex pharmacokinetics; enormous *Cl* and V_d (unaffected by malaria); blood concentration profile determined by distribution processes in malaria; $t_{1/2}$: 1–2 months	As for quinine but acts slightly earlier in asexual cycle	*Common:* Nausea, dysphoria, pruritus in dark-skinned patients, postural hypotension, slight ECG QTC prolongation *Rare:* Accommodation difficulties, keratopathy, rash *Note:* Bitter taste, well tolerated	*Acute:* Hypotensive shock (parenteral), cardiac arrhythmias, neuropsychiatric reactions *Chronic:* Retinopathy (cumulative dose, >100 g), skeletal and cardiac myopathy
Piperaquine	Adequate oral absorption, may be enhanced by fats; similar pharmacokinetics to chloroquine; $t_{1/2}$: 21–28 days	As for chloroquine, but retains activity against multidrug-resistant *P. falciparum*	Epigastric pain, diarrhea, slight ECG QT_c prolongation	None identified
Amodiaquine	Good oral absorption; largely converted to active metabolite desethylamodiaquine	As for chloroquine	Nausea (tastes better than chloroquine)	Agranulocytosis; hepatitis, mainly with prophylactic use; should not be used with efavirenz
Primaquine	Complete oral absorption; active metabolite not known; $t_{1/2}$: 5–7 h	Radical cure; eradicates hepatic forms of *P. vivax* and *P. ovale;* kills all stages of gametocyte development of *P. falciparum*	Nausea, vomiting, diarrhea, abdominal pain, hemolysis, methemoglobinemia	Massive hemolysis in subjects with severe G6PD deficiency
Mefloquine	Adequate oral absorption; no parenteral preparation; $t_{1/2}$: 14–20 days (shorter in malaria)	As for quinine	Nausea, giddiness, dysphoria, fuzzy thinking, sleeplessness, nightmares, sense of dissociation	Neuropsychiatric reactions, convulsions, encephalopathy
Halofantrine[a]	Highly variable absorption related to fat intake; $t_{1/2}$: 1–3 days (active desbutyl metabolite $t_{1/2}$: 3–7 days)	As for quinine	Diarrhea	Cardiac conduction disturbances; atrioventricular block; marked ECG QT_c interval prolongation; potentially lethal ventricular tachyarrhythmias
Lumefantrine	Highly variable absorption related to fat intake; $t_{1/2}$: 3–4 days	As for quinine	None identified	None identified
Artemisinin and derivatives (artemether, artesunate)	Good oral absorption, slow and variable absorption of IM artemether; artesunate and artemether biotransformed to active metabolite dihydroartemisinin; all drugs eliminated very rapidly; $t_{1/2}$: <1 h	Broader stage specificity and more rapid than other drugs; no action on liver stages; kills all but fully mature gametocytes of *P. falciparum*	Reduction in reticulocyte count (but not anemia); neutropenia at high doses; in some cases, delayed anemia after treatment of severe malaria with hyperparasitemia	Anaphylaxis, urticaria, fever
Pyrimethamine	Good oral absorption, variable IM absorption; $t_{1/2}$: 4 days	For blood stages, acts mainly on mature forms; causal prophylactic	Well tolerated	Megaloblastic anemia, pancytopenia, pulmonary infiltration
Proguanil (chloroguanide)	Good oral absorption; biotransformed to active metabolite cycloguanil; $t_{1/2}$: 16 h; biotransformation reduced by oral contraceptive use and in pregnancy	Causal prophylactic; not used alone for treatment	Well tolerated; mouth ulcers and rare alopecia	Megaloblastic anemia in renal failure
Atovaquone	Highly variable absorption related to fat intake; $t_{1/2}$: 30–70 h	Acts mainly on trophozoite blood stage	None identified	None identified
Tetracycline, doxycycline[b]	Excellent absorption; $t_{1/2}$: 8 h for tetracycline, 18 h for doxycycline	Weak antimalarial activity; should not be used alone for treatment	Gastrointestinal intolerance, deposition in growing bones and teeth, photosensitivity, moniliasis, benign intracranial hypertension	Renal failure in patients with impaired renal function (tetracycline)

[a]Halofantrine should not be used by patients with long ECG QT_c intervals or known conduction disturbances or by those taking drugs that may affect ventricular repolarization—e.g., quinidine, quinine, mefloquine, chloroquine, neuroleptics, antiarrhythmics, tricyclic antidepressants, and some antihistamines. [b]Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age.

Abbreviations: *Cl*, systemic clearance; ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; V_d, total apparent volume of distribution.