TABLE 41.1 Pharmacokinetic Properties of the Major Antimalarials

DRUG (METABOLITE)	C_{MAX}	T_{MAX} (h)	AUC	K_A (per h)	V/F (L/kg)	CL/F (L/h per kg)	$T_{½}$
Intravenous artesunate (dihydroartemisinin)	11,346–29,681 ng/mL (1279–3011 ng/mL)	— (0.01–0.2)	558–1146 ng/mL × h (739–2559 ng/mL × h)	— (—)	0.08–0.24 (0.47–1.01)	1.63–4.26 (0.73–2.16)	0.03–0.19 h (0.3–1.1 h)
Rectal artesunate (dihydroartemisinin)	269–507 ng/mL (682–896 ng/mL)	0.8–0.9 (1.5–2.3)	692 ng/mL × h (2402–2786 ng/mL × h)	0.3 (0.7)	2.1 (2.1–4.4)	6.0 (2.2–2.64)	0.9 h (0.7–1.3 h)
Oral artesunate (dihydroartemisinin)	51–244 ng/mL (251–488 ng/mL)	0.5 (2.0)	113–232 ng/mL × h (740–1671 ng/mL × h)	3.3 (1.19–4.27)	6.8 (2.3–4.6)	19.2 (0.6–4.0)	0.36 h (0.64–2.5 h)
Oral artemether (dihydroartemisinin)	34–186 ng/mL (101–165 ng/mL)	1.0–2.0 (1.0–3.0)	65.6–211 ng/mL × h (357–604 ng/mL × h)	— (—)	49.5 (7.8)	25.9 (4.5)	1.5–3.9 h (1.3–1.9 h)
Lumefantrine	5.72–25.7 μg/mL	4.0–544.0	210–636 μg/mL × h	0.06–0.17	3.7	0.12	32.7–79.2 h
Piperaquine	568 ng/mL	5.7	46.9–56.4 μg/mL × h	0.08–0.72	164–614	0.85–1.85	12–28 days
Pyronaridine	130 ng/mL	2.4–3.2	29400 ng/mL × h	0.7	72	0.9	14–18 days
Mefloquine	1.62–2.70 μg/mL	15.0–45.0	307.2–1497 μg/mL × h	0.292	8.14–31.8	0.017–0.174	8.5–19.3 days
Amodiaquine (desethylamodiaquine)	14.1–15.5 ng/mL (235–1185 ng/mL)	– (46.9–47.9)	(28.9–44.3 μg/mL × h) (–)	— (0.13–0.87)	322.7 (75.2–123)	14 (0.61–0.86)	3.3 h (104–216 h)
Chloroquine (desethylchloroquine)	283–1430 ng/mL (89–220 ng/mL)	6.5–6.9 (–)	37–140 μg/mL × h (44–64 μg/mL × h)	0.14 (—)	31.8–154 (—)	0.23–0.80 (—)	4.5–9.7 days (7.3–8.5 days)
Quinine	4–15.3 μg/mL	2.0–16.1	52.6–332 μg/mL × h	0.93–3.50	0.53–1.84	0.05–0.138	7.0–19.7 h
Atovaquone	2.07–13.3 μg/mL	5.1	63–663 μg/mL × h ($AUC_{48h–\infty}$)	0.26–0.46	4.7–10.2	0.07–0.32	31.3–72.9 h
Proguanil (cycloguanil)	363–750 ng/mL (26–67 ng/mL)	4.5–5.2 (6.4–6.9)	5.7–13.5 μg/mL × h ($AUC_{48h–\infty}$) (0.71–1.8 μg/mL × h) ($AUC_{48h–\infty}$)	0.41–0.51 (—)	15.8–29.7 (—)	0.76–1.23 (—)	8.0–17.6 h (6.4–22.6 h)
Primaquine 15 mg daily for 14 days (carboxyprimaquine)	50.7–57.7 ng/mL (291–432 ng/mL)	2.2–2.3 (2.6–7.3)	480–547 ng/mL × h —	— (—)	4.8–5.1 (—)	0.2–0.5 (—)	5.6–6.4 h (21.8 h)
Primaquine 45 mg, single dose (carboxyprimaquine)	167 ng/mL (890 ng/mL)	2.0 (6.1)	— (12,737 ng/mL × h)	— (—)	— (—)	0.5 (—)	6.1 h (—)
Tafenoquine 300 mg single dose	320 ng/mL	15 days	98 μg/mL × h (0–60 days)	0.23	>20	0.06	15 days
Pyrimethamine	280 ng/mL	12.0–19.8	38.0–89.1 μg/mL × h	—	4.25–4.46	0.0174–0.0417	2.8–3.4 days
Sulfadoxine	63.9–130 μg/mL	5.7–13.5	—	0.3	0.242–3.13	0.00068–0.00190	4.1–8.9 days

AUC, Area under the concentration-time curve; *CL/F,* apparent total clearance after oral administration; C_{max}, maximum plasma concentration; K_a, first-order absorption rate constant; $t_{½}$, terminal elimination half-life t_{max}, time after administration to maximum plasma concentration; *V/F,* apparent volume of distribution.
Only metabolites that have been reported are included in this table; some antimalarial agents have active metabolites (e.g., desbutyl-lumefantrine for lumefantrine) that have not been reported in any of the studies summarized here.
Modified in part from http://www.who.int/malaria/publications/atoz/9789241502061/en/; Table 3.1, p. 62.

in young children[29,30] The kinetics of DHA are also modified significantly in late pregnancy, with oral bioavailability reduced by 23%[31]; plasma concentrations are significantly lower than those observed in nonpregnant women.[26] Further dose-optimization studies in pregnant women may be necessary.

Clinical Use

Comparative clinical studies have shown the artemisinin compounds to act faster than any other licensed antimalarial, with typical fever clearance times being approximately 20 hours and parasite clearance achieved within 48 hours.[32] Although this class of drugs is extremely potent, treatment success if administered without a partner drug is dependent upon the duration of therapy, rather than on the dose or dose regimen. Because these compounds are rapidly eliminated, a prolonged course (minimum, 7 days) of monotherapy is required to effect cure,[33] particularly in patients presenting with high initial parasitemia.[34] For this reason World Health Organization (WHO) recommends that artemisinin derivatives always be administered with a longer half-life partner drug to improve cure rates,[35] so-called artemisinin combination therapy (ACT).

Combination regimens with an artemisinin derivative offer several inherent benefits. The rapid clinical response can improve the tolerability and absorption of the combination partner drug, which can often be compromised in an acutely febrile patient.[36,37] The rapid reduction of the pathogen biomass achieved with an artemisinin derivative also reduces the number of asexual parasites exposed to the second drug, thereby reducing the chances of a resistant mutant emerging during treatment.[38] The sustained clinical efficacy of several ACTs suggests that this strategy may have has indeed slowed the rise of antimalarial resistance in areas where use has been widespread.[39] A combination treatment regimen also serves to protect the artemisinin compounds because neither drug will be exposed to the parasites alone.[40–43] Artemisinin derivatives have the additional benefit of reducing the production of gametocytes, the sexual stages of the parasite.[44] Because recrudescent infections are associated with an increase in gametocyte carriage, the reduction in their carriage after ACT may help to slow the emergence of resistance and reduce malaria transmission in settings of low endemicity.[45]

More than 80 malaria-endemic countries have now endorsed the use of ACT as the first treatment of uncomplicated malaria, with huge clinical experience supporting their safety and efficacy.[35] WHO recommends six ACTs for the treatment of uncomplicated falciparum malaria: artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, DHA + piperaquine, artesunate + sulfadoxine-pyrimethamine, and artesunate + pyronaridine.[35]

Artemether-lumefantrine is a fixed-dose combination registered by regulatory authorities in Europe, the United States, and Australia

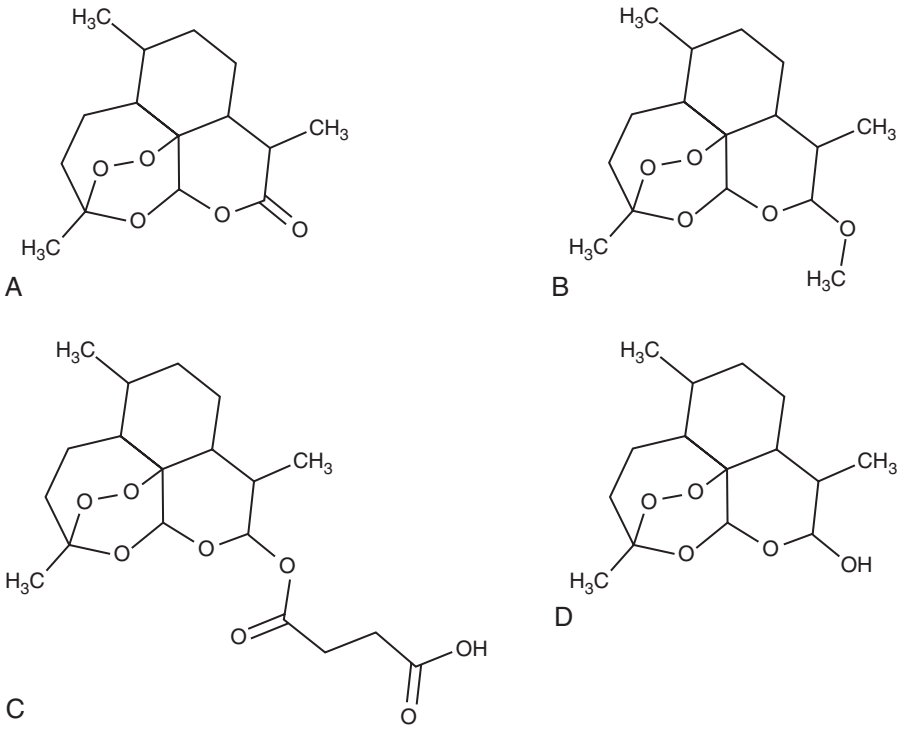

FIG. 41.2 Structures of artemisinin derivatives. (A) Artemisinin. (B) Artemether. (C) Artesunate. (D) Dihydroartemisinin.

(under several trade names, including Coartem and Riamet), where it is approved for the oral treatment of malaria. In addition, four other fixed-dose ACTs have been licensed through the European Drug Agency: DHA-piperaquine (Eurartesim), artesunate-amodiaquine (Winthrop), artesunate-mefloquine (Mefliam plus), and artesunate-pyronaridine (Pyramax), although to date their use in nonendemic countries is limited. The combination artesunate plus sulfadoxine-pyrimethamine is available in a blister pack formulation. The synthetic trioxolane OZ277 has been combined with piperaquine (Synriam) and is now available for use in several African countries, although there is sparse data available from phase III clinical trials.[4]

Severe Malaria

The rapid action and broad-stage specificity of the artemisinin derivatives are critically important for their role in the treatment of severe malaria and for prevention of the development of severe disease. Patients with high parasitemia (>4%) are at significantly greater risk of mortality compared with those with lower parasitemia. Oral artesunate results in faster parasite clearance compared with IV quinine, with potential to arrest the progression to severe disease.[46] The clinical benefits of accelerated parasite clearance have been highlighted in patients with severe malaria in two multicenter, randomized clinical trials comparing IV quinine to artesunate. The first, conducted at four sites in Southeast Asia in 1461 patients, highlighted a 35% reduction in case fatality with IV artesunate (from 22%–15%).[47] The second, conducted in 5425 patients enrolled at 11 African sites, involved a greater proportion of children and showed a 22% reduction in fatality (from 10.9%–8.5%).[48] A meta-analysis of these results, together with other smaller clinical trials, highlights overwhelming evidence for the clinical efficacy of IV artesunate in reducing the mortality from severe malaria in an endemic setting (odds ratio [OR] 0.69; 95% confidence interval [CI], 0.57 to 0.87]).[48]

Artesunate can be given by slow IV or IM injection, at an initial dose of 2.4 mg/kg (≈140 mg in adults), followed by 2.4 mg/kg at 12, 24, and 48 hours, with further daily doses if required. In view of the reduced concentration of DHA after parenteral administration of artesunate to young children, the recommended dose in patients weighing less than 20 kg is 3 mg/kg of artesunate.[35] Once oral treatment can be tolerated, treatment can be changed to appropriate ACT to ensure complete eradication of any remaining parasites. In addition to parenteral formulations, the rapid absorption of rectal artesunate resulting in high plasma concentrations gives it significant advantages over the other artemisinin derivatives in prehospital treatment of malaria.[49] In settings without ready access to parenteral therapy, in children less than 6 years an artesunate suppository at a dose of 10 mg/kg may be administered before reaching a health care facility where more intensive treatment can be given.[50]

Resistance

The artemisinin derivatives have been in clinical use in China and Cambodia for almost 40 years, whereas deployment in the rest of the world has increased substantially over the past 15 years. The first concerns of artemisinin resistance arose from clinical studies in western Cambodia,[51] where delayed parasite clearance rates were recognized as the earliest indication of declining efficacy[52,53]). Large multicenter clinical studies have highlighted the variation in clearance half-lives across the Greater Mekong, ranging from more than 6 hours in western Cambodia and in Srisaket in Thailand, to 3 hours in Vietnam and Myanmar, 2.5 hours in Bangladesh, and more than 2 hours in a variety of African sites.[54] The variation in parasite clearance rates is proposed to be due to reduced activity against immature ring stages of the parasite.[55] Molecular studies have identified a correlation between artemisinin resistance and mutations of the kelch protein gene on chromosome 13 (*kelch 13* [K13]).[54,56] In Cambodia, the epicenter of drug resistance, 17 K13 mutations have been identified. More recent studies in Myanmar have identified further relevant mutations with different geographic distribution.[57] Other molecular surveys have demonstrated that spontaneous K13 mutations have arisen in many endemic locations[58] although not all of these polymorphisms are associated with reduced susceptibility.

The public health consequences of declining treatment efficacy, particularly in areas of high transmission, are alarming, especially when they are combined with resistance to the partner drug. This threat is heightened by the fact that no other antimalarial medicines are currently available that offer the same level of efficacy and tolerability as ACTs.

Toxicity

The artemisinin drugs have an excellent toxicity profile, the most commonly reported adverse effects being nausea, vomiting, and diarrhea, all of which are frequently reported during an acute malaria.[59,60] No

differences in the incidence of possible clinical adverse reactions have been noted between derivatives. There have been a few cases of acute urticaria and anaphylaxis after oral artesunate and artemether alone[61] or in combination[59]; readministration to these individuals should be avoided.

High doses of the lipophilic members of this family, such as artemether, have been associated with neurologic toxicity in animal studies involving rodents, dogs, and monkeys.[62–65] The pattern of neuronal damage is unusual, preferentially affecting the brainstem, in particular the reticular formation, vestibular system nuclei, and trapezoid nucleus. In animals manifestation includes gait disturbance; loss of spinal, brainstem, and pain responses; and cardiorespiratory depression. However, prolonged exposure at high doses (>15 mg/kg/day for more than 15 days) through parenteral administration is required to elicit this toxicity, and the risk is far greater after parenteral rather than oral administration.

There is no conclusive evidence of neurotoxicity in humans exposed to artemisinin derivatives at doses used in clinical practice (generally less than a total of 12 mg/kg). Several studies have reported neurologic abnormalities after artesunate treatment of patients with malaria, some of which have been attributed to artemisinin neurotoxicity[66–68]; however, the doses of drug administered suggest that drug toxicity would be unlikely. Cerebellar dysfunction, although rare, is a well-recognized complication of malaria[69]; hence these reports may reflect the presentation of patients with postmalarial neurologic syndrome (PMNS) rather than drug toxicity.[70]

Artemisinin derivatives have been used in several million patients over the past 20 years, with more than 10,000 enrolled in clinical trials and more than 300 patients undergoing formal neurophysiologic testing. Despite this, there have been no convincing clinical reports of neurotoxicity reliably associated with these drugs.[59,71] These studies have been supported further by the analysis of patients undergoing audiometry and auditory-evoked responses, which have also failed to reveal significant neurologic pathology.[72,73] Large prospective studies of patients with recurrent exposure to coartemether are in progress.

Cardiotoxicity does not appear to be a significant issue with the artemisinins; electrocardiographic changes are confined to minor QT prolongation, sinus bradycardia, and a few cases of transient first-degree heart block.[74] Hematologic abnormalities have been noted, particularly mild transient neutropenia (1.3%), when doses of artesunate in excess of 18 mg/kg total dose have been administered. Delayed onset of anemia has been reported in patients treated with IV artesunate for severe malaria.[75,76] The nadir occurs 8 to 28 days after treatment but generally improves within 4 to 6 weeks. The underlying mechanism is unclear but has been postulated to be due to artesunate killing malaria parasites without destroying the red blood cell, resulting in more deformable cells surviving the acute infection but with a shorter life span.[77] *It would be prudent to check the hemoglobin in such cases about 2 weeks after commencing IV artesunate therapy.*

Embryotoxicity and fetal resorption, but not teratogenicity, have been reported in animal studies at relatively low doses of artemether (7.5–15 mg/kg/day).[78] However, clinical studies from the Thai-Myanmar border and The Gambia have indicated that artesunate and artemether are well tolerated in pregnancy, with no evidence of an increased risk of abortion, stillbirth, congenital abnormality, or premature delivery.[79–82] In one study, where infants were monitored in the first year of life, normal developmental milestones were attained.[83]

Available data are reassuring for the administration of the artemisinin derivatives in later pregnancy,[84] and more recent clinical studies have reported that this safety extends to their use in the first trimester.[85] WHO antimalarial treatment guidelines committee recently revised the guidelines to recommend ACT for uncomplicated *P. falciparum* malaria to be extended to women in all stages of pregnancy, with artemether-lumefantrine being the preferred drug in the first trimester in view of it having the largest amount of safety data available.

ARTEMISININ PARTNER DRUGS

Lumefantrine

Lumefantrine (Fig. 41.3) is an aryl-amino alcohol, currently only available as a fixed-dose oral formulation, combined with artemether (coartemether: 20 mg of artemether and 120 mg of lumefantrine). Artemether and lumefantrine have complementary activity—the potent but short-lived antimalarial activity of artemether resulting in a rapid reduction of parasite biomass over the first 3 days of treatment and the longer-acting lumefantrine providing sustained antimalarial activity to kill the residual blood-stage parasites. The combination has become one of the most highly used ACTs, with more than 3 billion treatments dispensed in malaria-endemic countries over the past decade.

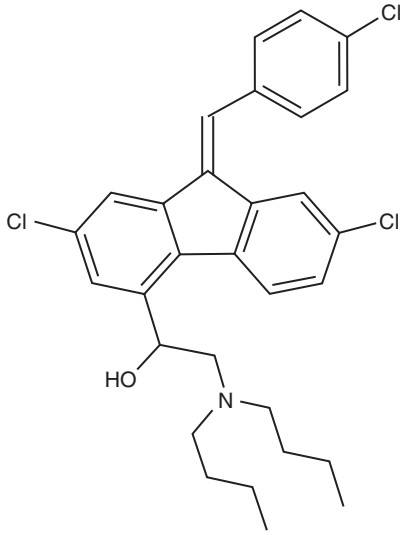

FIG. 41.3 **Structure of lumefantrine.**

The activity of lumefantrine is well documented against the erythrocytic stages of both *P. falciparum* and *P. vivax,* but does not extend to activity against gametocytes, hypnozoites, or the preerythrocytic stages. Although the mechanism of action is incompletely understood, it is thought that lumefantrine and other members of this class exert their antimalarial effect in the parasite's acid food vacuole by interacting with heme. Desbutyl-benflumetol, the putative metabolite of lumefantrine, has significantly higher blood schizonticidal activity compared with lumefantrine.

Pharmacokinetics

After ingestion, lumefantrine is slowly and erratically absorbed with peak concentrations occurring within 4 to 10 hours. Bioavailability is highly variable and reduced significantly during the acute phase of the infection[86] but increases when administered with food.[87] Only a small amount of fat is necessary to increase bioavailability, with as little as 36 mL of milk (corresponding to 1.2 g of fat) being sufficient for a clinically relevant increment (up to 16-fold) in blood concentrations.[88] Absorption is dose limited and results in the need for twice-daily dosing over 3 days rather than once-daily dosing. Lumefantrine is extensively and rapidly distributed to body tissues and highly protein bound (90%). It is metabolized predominantly by the liver and eliminated through the bile,[87] with a terminal elimination half-life of 3 to 6 days in patients with malaria. Pregnancy is associated with a significantly faster terminal elimination half-life compared with nonpregnant patients (49 vs. 77 hours, respectively).[89] The principal pharmacokinetic determinant of lumefantrine efficacy in patients with malaria is the area under the concentration-time curve (AUC), which is correlated closely with the plasma lumefantrine concentrations on day 7.[90,91]

Clinical Use

Artemether-lumefantrine is registered in many countries for the treatment of uncomplicated malaria, especially of multidrug-resistant *P. falciparum* infection. In view of its excellent tolerability and efficacy against all species of plasmodia and most multidrug-resistant isolates, it has been proposed as standby medication for travelers to countries endemic for malaria.

The dose for adults weighing more than 35 kg is four tablets of the fixed-dose combination per dose (total per dose: artemether 80 mg, lumefantrine 480 mg) given twice daily over 3 days (0, 8, 24, 36, 48, and 60 hours). Patients should be instructed to take their medication with milk or a fat-containing food, such as maize porridge with vegetable oil, particularly on the second and third day of treatment.

The efficacy and safety of artemether-lumefantrine in children weighing 5 to 10 kg is similar to that in older children.[92,93] A dispersible, pediatric tablet, containing 20 mg of artemether and 120 mg of lumefantrine, has been developed for use in infants and young children[35] and shows a similar efficacy and safety profile to that after administration of the crushed standard tablet.[94] The dosing schedule is the same as that for adults, with the body weight–adjusted doses stratified into three groups: 25 to 35 kg, 3 tablets per dose; 15 to 25 kg, 2 tablets per dose; and 5 to 15 kg, 1 tablet per dose. The child should take the medication with a small quantity of fat. A pooled analysis revealed that young children are underdosed with the current dosing schedule, although dosing recommendations have yet to be revised to address this.[95]

Coadministration of antiarrhythmics, β-blockers, macrolides, quinolones, antidepressants, antifungals, and grapefruit juice should be avoided. However, there is no evidence of harmful interactions after coadministration with these drugs. Mefloquine reduces plasma concentrations of lumefantrine by 30% to 40%,[96] whereas ketoconazole increases the AUC by 70%[97]; neither interaction is considered sufficient to warrant altering dosing.

Lumefantrine has good activity against chloroquine-resistant (CQ-R) strains of *P. falciparum* and *P. vivax*.[8] Both polymorphisms and copy number of the *pfmdr1* gene modulate susceptibility to lumefantrine[91,98] and are under selective pressure, with the *86N* allele (wild-type) significantly more prevalent in patients failing treatment.[99,100] A pooled analysis of data from more than 7000 patients demonstrated that *pfmdr1* amplification is an independent risk factor for recrudescence in patients treated with artemether-lumefantrine.[101]

Toxicity

Artemether-lumefantrine has an excellent toxicity profile. The most commonly reported adverse effects are nausea, vomiting, and diarrhea.[102] Pruritus and rash occur in less than 2% of patients. In contrast to the significant cardiotoxicity of halofantrine, despite its structural similarity with lumefantrine, no significant prolongation of the QTc intervals has been observed after administration of coartemether.[96,102] Although data are generally lacking on potential adverse interactions between lumefantrine and other drugs, there is no evidence of an interaction between lumefantrine and either mefloquine[96] or quinine.[103]

Although lumefantrine has not been formally evaluated sufficiently to recommend its widespread use in pregnancy, animal reproductive toxicity studies have failed to demonstrate mutagenic or embryotoxic properties in doses up to 1000 mg/kg, and the coformulation with artemether has been recommended as suitable for treatment of *P. falciparum* infection in pregnancy. Increasing amounts of accumulating data indicate that artemether-lumefantrine is better tolerated than conventional quinine, which is associated with hypoglycemia and poor adherence to a 7-day regimen.[84,104,105] Rates of recurrence of malaria after coartemether are high in pregnant women, a likely reflection of the increased rate of elimination of lumefantrine.[106] A recent multicenter, randomized trial demonstrated inferior cure rates compared with DHA-piperaquine.[107] This is likely associated with lower serum concentrations of lumefantrine.[106,108,109] Although studies are underway, there are as yet no formal recommendations for safe dose adjustment to overcome this. Current WHO guidelines do not preclude lactating mothers from taking artemether-lumefantrine because the amount of either active antimalarial drug entering breast milk is small, with no associated evidence of toxicity to the baby.[35]

Piperaquine

Piperaquine is a bisquinoline 4-aminoquinoline antimalarial structurally related to CQ. It was synthesized independently in France and China in the 1960s[110] and widely used for malaria control activities in China in the 1970s and 1980s.[111] In the 1990s piperaquine was repurposed as a partner drug in artemisinin-based combination therapy, and resulted in the development of a combination formulation of DHA plus piperaquine, with each tablet containing 40 mg DHA and 320 mg piperaquine phosphate (DHP). The mechanism of action of piperaquine has not been well studied but is likely to be similar to those of drugs of the same class.[111]

Pharmacokinetics

The pharmacokinetic properties of piperaquine are similar to those of CQ. It has a large volume of distribution, ranging from 103 to 716 L/kg, values that are significantly larger even than comparable drugs such as CQ.[112–114] It has a long terminal elimination half-life of 22 days in adults and 20 days in children.[115] The prolonged half-life results in a beneficial posttreatment prophylactic period, estimated to be about 28 days, and protects against both *P. vivax* and *P. falciparum*. Although early recurrent infections are reduced, infections treated with DHP are more likely to produce gametocytes than artemether-lumefantrine, an observation hypothesized to reflect the lower dosing of artemisinin derivative in DHP (total ≈7.5 mg/kg of DHA compared with ≈11.5 mg/kg of artemether in artemether-lumefantrine). Body weight influences clearance and volume parameters significantly, resulting in lower piperaquine exposures in small children (<25 kg) compared with larger children and adults,[116] and this is associated with a higher risk of recrudescence and earlier reinfection.[117]

Piperaquine is highly lipophilic, and its oral bioavailability is approximately doubled by administration with a high-fat meal.[118,119] However, data on the food effect of bioavailability of piperaquine are conflicting.[113,120,121] In a study carried out in Papua New Guinea,[122] a surprisingly low efficacy of DHP was reported (88% at day 42), significantly lower than that for artemether-lumefantrine. However, the difference had wide CIs and was apparent at day 28 but not day 42. This reduced efficacy is in contrast to other studies carried out in Africa[123–125] and Asia,[126,127] where DHP had similar or higher efficacy to other ACTs.

Clinical Use

Several fixed-dose formulations of DHP have been marketed, although only Eurartesim has been approved by the European Drug Agency. Eurartesim is available in tablets of two strengths, either 20/160 or 40/320 mg of DHA-piperaquine, respectively. It is used for the treatment of uncomplicated malaria, administered over 3 consecutive days for a total of three doses taken at the same time each day. The recommended dose is 4/18 mg/kg, once daily for 3 days (equivalent to 3–4 40/320 tablets for adults). Some manufacturers recommend four doses (at 0, 6–8, 24, and 32 hours), although there is no evidence that this regimen has any better efficacy than the simpler once-daily dosing. A large pooled analysis of more than 20 clinical trials highlighted the excellent efficacy of DHP, although a slightly higher risk of treatment failure has been identified in children age 1 to 5 years.[117] In 2015 WHO treatment guidelines revised the dose in children to be less than 25 kg, to receive a minimum of 2.5 mg/kg per day of dihydroartemisinin and 20 mg/kg per day of piperaquine, daily for 3 days.[35] Development of a pediatric formulation is underway.

Resistance

Piperaquine has potent activity against highly CQ-R *P. falciparum*[115] and *P. vivax*.[8] Widespread use of piperaquine has mostly been confined to the use in combination with dihydroartemisinin (DHP) introduced into national policy in Cambodia and Indonesia. Although initially showing excellent efficacy against all species of malaria,[126] reports of declining efficacy against *P. falciparum* began to emerge in 2010, although these were almost exclusively in the Greater Mekong region, on a background of the K13 mutations associated with artemisinin resistance.[128,129] Subsequent genomic studies have implicated amplification of the plasmepsin 2 gene and a single nucleotide polymorphism of the exo-E415G on chromosome 13, both of which appear to correlate with clinical efficacy.[130,131]

Toxicity

DHP appears to be better tolerated than artesunate-mefloquine administered with similar tolerability to artemether-lumefantrine

and amodiaquine-artesunate.[115,132] The main side effects reported are gastrointestinal (GI) disturbance such as diarrhea,[126] although this varies considerably according to geographic region.

Electrocardiographic effects of piperaquine have been specifically evaluated in two studies.[133,134] Both demonstrated minor lengthening of the corrected QT interval during treatment (between 11 and 14 ms). Very few patients experienced a prolongation that could be regarded as clinically significant (>60 ms). Therefore, although statistically significant, the QT prolongation observed after piperaquine therapy is unlikely to be clinically significant. European regulatory authorities have, however, required that DHP not be administered with food (to reduce peak concentrations) and caution that prior electrocardiographic monitoring be undertaken in those at risk of QT prolongation.

Pyronaridine

Pyronaridine is a Mannich base antimalarial synthesized in China in the 1970s.[135,136] It demonstrates potent in vitro activity against erythrocytic stages of *P. falciparum*[137–139] and *P. vivax.*,[140] including against parasites with high-grade CQ resistance.[141–143] A fixed-dose formulation of pyronaridine and artesunate combined in a 3:1 ratio has been developed for treatment of multidrug-resistant uncomplicated malaria (Pyramax). This novel ACT was licensed by the European Medicines Agency in 2012; it has been reviewed comprehensively.[144]

Clinical trials have shown potent efficacy of monotherapy against multidrug-resistant falciparum malaria,[145–147] as well as *Plasmodium ovale* and *Plasmodium malariae*.[146] The early therapeutic response was faster when pyronaridine was combined with artesunate.[148] Subsequent multicenter clinical trials have demonstrated excellent efficacy against multidrug-resistant strains of *P. falciparum*[149,150] and *P. vivax*.[151]

Pharmacokinetics

The pharmacokinetic profile of pyronaridine suggests that peak concentrations after single administration are reached within 1 hour, with a large volume of distribution (907 L) and a terminal elimination half-life of between 10 and 13 days.[152] The pharmacokinetic profile in children is similar, with a slightly faster elimination (half-life 6–9 days).

Clinical Use

Pyronaridine is available in combination with artesunate (Pyramax) as an alternate ACT for the treatment of acute, uncomplicated malaria infection caused by *P. falciparum* or by *P. vivax* in adults and children weighing 20 kg or more. Pyramax comes in tablets for adults with pyronaridine 180 mg and artesunate 60 mg. The dose for adults 65 to 90 kg is four tablets once daily for 3 days. A pediatric formulation containing 60 mg pyronaridine and 20 mg artesunate has also been developed with large clinical trials completed.[145,153]

Toxicity

Pyronaridine is generally well tolerated, the most common side effects being headache, vomiting, abdominal pain, bradycardia, and hypoglycemia. Early animal studies and early clinical trials suggested that pyronaridine may cause transient hepatotoxicity.[149–151] However, in a recent study the incidence of adverse effects, particularly hepatotoxicity after repeated courses of pyronaridine-artesunate, was not increased.[154]

Amodiaquine

Amodiaquine (AQ) (Fig. 41.4) is a 4-aminoquinoline that was widely used for prevention of malaria until the mid-1980s, when fatal adverse drug reactions described in travelers using AQ as prophylaxis[155] resulted in a dramatic decrease in its use for these indications. However, reevaluation of the drug for treatment rather than prophylaxis[156] resulted in increased recognition that the drug is not significantly more toxic than CQ when used for treatment. Its activity against CQ-R parasites gives it an important role in the antimalarial pharmacopoeia. However, this activity against CQ-R parasites shows significant geographic variation, activity being greater against isolates from Africa,[157–159] whereas those from Southeast Asia, South America, and Papua New Guinea display high levels of AQ resistance.[160] The apparent geographic specificity of AQ resistance may be due to differences among the haplotypes of the parasite *pfcrt* gene in these locations.[161] The mechanism of action of AQ is believed to be similar to that of CQ (see later).

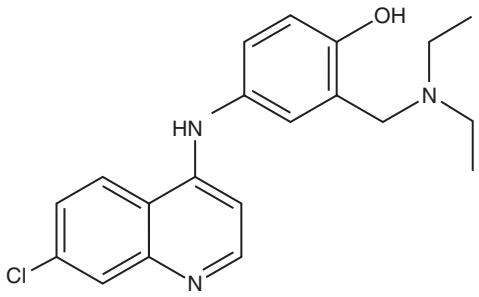

FIG. 41.4 Structure of amodiaquine.

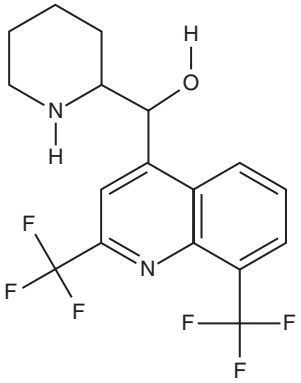

FIG. 41.5 Structure of mefloquine.

Pharmacokinetics

In contrast to CQ, AQ has a relatively short half-life (5 hours), being rapidly cleared by the liver by the action of CYP2C8 to an active metabolite, desethylamodiaquine AQ. The half-life of this metabolite has been variously estimated to be 1 to 3 weeks in adults and 3 to 12 days in children. Thus desethylamodiaquine provides approximately 100-fold-higher total drug exposure than AQ and therefore contributes most of the antimalarial effect of AQ.[162] Polymorphism of this enzyme may be a factor in drug interactions.

Clinical Use

Amodiaquine is used principally in a fixed-dose coformulation with artesunate (so-called AS/AQ). In two trials undertaken in sub-Saharan Africa, AS/AQ had superior efficacy to artemether-lumefantrine, with fewer episodes or recurrent parasitemia.[163,164] Although amodiaquine retains efficacy against CQ-R *P. vivax*,[8] recurrence rates after AQ monotherapy and AQ + artesunate are high.[165,166]

Toxicity

The most important adverse effects of AQ are hepatotoxicity (1/15,000 exposures) and bone marrow toxicity (1/2200 exposures; fatality rate, 1/31,000). Of note, none of these toxic effects have been reported when AQ has been used for malaria treatment but only in more prolonged use as a prophylactic agent. However, the actual incidence of such serious side effects in the setting of treatment is unknown. An important recently reported side effect is the significant risk of severe neutropenia in human immunodeficiency virus–infected children treated for malaria with artesunate-AQ.[167]

Mefloquine

Mefloquine (Fig. 41.5) is a chiral quinoline methanol. It is active against the asexual erythrocytic stages of malarial parasites but not against sporozoites, liver-stage parasites, or gametocytes. Mefloquine forms a complex with heme that may be toxic to the parasite,[168] although its mechanism of action is believed to be distinct from that of CQ. CQ-R parasites are more sensitive to mefloquine and vice versa.[98]

Pharmacokinetics

Mefloquine is only available as an oral tablet formulation. Absorption is adversely affected by vomiting and diarrhea but significantly enhanced when administered with or after food.[169] The mean absorption half-life of mefloquine after a single oral dose is 2.1 hours in healthy volunteers and 5.4 hours in patients with uncomplicated falciparum malaria.[170] About 98% of the drug binds to protein.[171] The terminal elimination half-life is 14 to 28 days. The apparent volume of distribution is compatible with plasma protein binding of greater than 98%.[171] Pharmacokinetic parameters are similar in single- and multiple-dose studies of healthy volunteers, suggesting that there are no significant changes in clearance when mefloquine is taken for prophylaxis. Mefloquine at a dose of 250 mg of the salt taken weekly reaches steady-state concentrations in 10 weeks without any indication of accumulation.[172] Mefloquine pharmacokinetics are highly stereoselective, with the (−) enantiomer demonstrating a significantly greater C_{max}, AUC, and longer elimination half-life than the (+) enantiomer.[173]

No dose adjustment is necessary in renal impairment or hemodialysis. Excretion of the drug and its metabolites is largely in the bile and feces. No studies have examined mefloquine disposition in patients with significant hepatic dysfunction, ascites, or cardiac failure. Because mefloquine is largely metabolized by the liver, the use of usual prophylactic doses over time may cause significant accumulation and consequent increased toxicity in patients with liver disease.

Clinical Use

Mefloquine is indicated for the treatment and prophylaxis of malaria, including CQ-R strains. Treatment regimens initially recommended a single dose of 15 mg/kg, although a higher dose (25 mg/kg) has been recommended to overcome declining efficacy. A combination with artesunate (4 mg/kg/day) as a 3-day regimen has been used in parts of Southeast Asia for almost 20 years although in areas of emerging artemisinin resistance the efficacy of this combination appears to be declining.[39,173a] A fixed-dose combination of artesunate-mefloquine has a target dose of mefloquine of 8 mg/kg per day for 3 days, which improves its tolerability and reduces the risk of early vomiting.[174,175] Mefloquine is under study as a component of so-called triple ACT to combat artemisinin resistance in the Greater Mekong subregion. Evidence indicates that its use in combination with piperaquine may result in better activity against DHP-resistant parasites.[130]

Resistance

High-grade mefloquine-resistant strains of *P. falciparum* have been documented in Southeast Asia, particularly the western border of Thailand, since the early 1990s. Cross-resistance of mefloquine with lumefantrine, halofantrine, and quinine has been documented.[176] *P. falciparum* isolates resistant to mefloquine have both increased copy number of the *pfmdr1* gene and increased expression of the gene product.[177]

Toxicity

The adverse effects of mefloquine have been the subject of much study. More than 20 million doses have been prescribed since 1984. Consistent with the frequency of side effects during other chemoprophylactic regimens, weekly mefloquine is associated with symptoms such as dizziness, nausea, and diarrhea in 20% of travelers.[178] These symptoms are usually mild and self-limiting. Dose-related drug-induced vomiting can be problematic, particularly in young children, in whom rates can reach 30% in infants younger than 2 years. When given as part of an ACT, vomiting can be reduced by delaying the administration of the mefloquine component of the ACT until day 1 or 2 or splitting the dose of mefloquine over 3 days.[175,179] Less serious side effects include rash, pruritus, and oral ulcers.[180] More serious dermatologic reactions have been reported but are exceptionally rare.

The most serious adverse effect of mefloquine is neuropsychiatric toxicity. This can develop at any time during prophylaxis or treatment, and symptoms range from mild to life threatening. The incidence of neuropsychiatric effects appears higher in Caucasians and Africans than in Asians and higher in women than men.[178] Although difficult to assess in the context of an infection that can itself cause profound neurologic disturbances, psychosis, depression, encephalopathy, convulsions, and other severe neuropsychiatric effects occur after the use of mefloquine for treatment of falciparum malaria, with a frequency of 1 : 200 to 1800 courses.[175,181] Symptoms typically resolve within 3 to 4 weeks.[178] Serious reactions similar to those seen after treatment courses can occur during prophylaxis, with rates of 1 : 10,000 to 20,000 courses reported in large trials.[180,181] Sleep abnormalities (e.g., insomnia, abnormal dreams) have occasionally been reported. Mefloquine should not be prescribed to patients with neuropsychiatric conditions, including depression, anxiety, psychosis, schizophrenia, and seizure disorder. If acute anxiety, depression, restlessness, or confusion develops during prophylaxis, the drug should be discontinued. Mefloquine-induced neurotoxicity can be difficult to distinguish from PMNS, which typically lasts 1 to 10 days and consists of acute confusion, psychosis, and tremor, with or without convulsions. PMNS has been reported to occur at a rate of 1 : 1000 patients[182] but appears to be more common among patients with severe malaria, with frequencies of PMNS being reported in 1 in 20. This late complication is almost 10 times more likely to occur after treatment with mefloquine than quinine.[182] In an analysis of neuropsychiatric outcomes among 367,840 US Armed Services members prescribed mefloquine, doxycycline, or atovaquone-proguanil as chemoprophylaxis between 2008 and 2013, the risk of incident anxiety, tinnitus, and posttraumatic stress disorder (PTSD) was higher among recipients of mefloquine (incidence rate ratios of 1.12, 1.81, and 1.83, respectively). A prior neuropsychiatric history resulted in an increased, but not statistically significant, risk for adjustment disorder, anxiety, insomnia, and PTSD among mefloquine recipients.[183] In contrast, in a study of the side effect profile of mefloquine for the treatment of uncomplicated malaria on the Thai-Myanmar/Cambodia borders among 19,850 patients receiving seven different regimens of mefloquine, serious neuropsychiatric side effects associated with mefloquine use were rare, especially among patients administered a split dose over 3 days (7.8/10,000 treatments).[175] Of note, re-treatment with mefloquine within 1 month of a course of therapy markedly increases the risk of adverse effects sevenfold, rising from 1 per 1217 to 1 per 173.[184] Of importance, the incidence of neurotoxicity is significantly higher after severe malaria (1/20), and thus the drug should not be used in this setting.

Mefloquine should not be used concurrently with quinine, quinidine, or drugs producing β-adrenergic blockade owing to the risk of electrocardiographic abnormalities or cardiac arrest. Administration of mefloquine with quinine or CQ may increase the risk of convulsions. Mefloquine may lower plasma levels of anticonvulsants.[185] Minor or inconsistent interactions have been observed between mefloquine and sulfadoxine-pyrimethamine, primaquine, metoclopramide, and oral contraceptives. Mefloquine has been shown to exert variable effects on ritonavir pharmacokinetics.

Although mefloquine prophylaxis is not recommended during pregnancy, the drug is probably safe and effective and discovery of pregnancy during mefloquine prophylaxis is not an indication for pregnancy termination.[186]

Chloroquine

CQ, a 4-aminochloroquine (7-chloro-4-[4-diethylamino-1-methylbutylamino] quinoline) (Fig. 41.6), was first synthesized in Germany in 1934 but not developed until after World War II.[187] Hydroxychloroquine

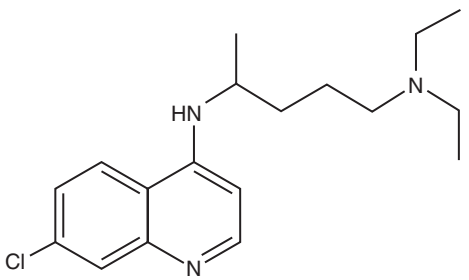

FIG. 41.6 Structure of chloroquine.

(Plaquenil), which differs from CQ only by hydroxylation at the end of the side chain, has identical antimalarial properties to CQ and is increasingly used in parts of the world where the availability of CQ is becoming limited. Hydroxychloroquine has antiinflammatory and antimalarial properties and is less prone to cause ocular toxicity than CQ among those receiving prolonged treatment,[188] and can be used interchangeably with CQ. CQ and other 4-quinoline antimalarials are only active against the blood stages of the parasite life cycle, during which hemoglobin is degraded.

CQ, a weak base, concentrates in the food vacuoles of intraerythrocytic parasites due to a pH gradient between the parasite cytoplasm and the acidic food vacuole of the parasite. Once it enters the food vacuole it is rapidly converted to a membrane-impermeable protonated form, where it is trapped. It binds to heme released after the parasite's digestion of host hemoglobin, preventing its conversion to the inert crystal hemozoin. It is the resulting accumulation of toxic heme monomers or the heme-CQ complex, or both, that is believed to kill the parasite.[189]

Pharmacokinetics

CQ is well absorbed whether given by oral, subcutaneous, or IM routes. Rectal bioavailability exceeds 90% but falls to 22% to 24% of the oral dose[190] unless a noncoated tablet is used, in which case plasma concentrations are only slightly lower than those found with oral administration.[191] CQ is 46% to 74% protein bound; it has an extremely large apparent volume of distribution and very long terminal half-life. As a consequence, a loading dose is required to yield effective plasma concentrations, and its pharmacokinetic profile is largely determined by its distribution rather than the elimination phase. Therapeutic drug levels in plasma are reached 2 to 3 hours after oral administration, with a mean initial half-life of 4 days. As plasma levels decline, the rate of excretion decreases, thus enabling once-weekly administration for prophylaxis. The estimated terminal elimination half-life is 45 to 55 days for CQ and 59 to 67 days for its active metabolite desethylchloroquine. Chloroquine is detectable in the urine for up to a year after drug administration.[192] Urinary excretion is the main route of elimination for both CQ and desethylchloroquine. The elimination half-life of CQ is significantly prolonged in chronic renal disease, with an associated increase in the AUC; hence a dose reduction is warranted in patients with renal insufficiency taking CQ for prophylaxis, although not required for acute malaria.[193]

Clinical Use

CQ remains the drug of choice for the treatment and prophylaxis of *P. falciparum* malaria in the few regions of the world where this species remains sensitive to this drug. (See Table 274.3 in Chapter 274 for chloroquine dosing.) Against sensitive parasites, CQ induces rapid parasite clearance only slightly slower than artemisinin drugs. CQ remains the treatment of choice for both prophylaxis and treatment of the nonfalciparum malarias, although this is under threat for *P. vivax* due to an increasing prevalence of CQ resistance in this species.[194] It lacks activity against sporozoites and mature gametocytes. Although CQ is not active against liver-stage infection, it may potentiate the activity of primaquine as a causal prophylactic agent.[195]

Resistance

CQ accumulates at concentrations 4 to 10 times lower in drug-resistant parasites compared with chloroquine-sensitive (CQ-S) parasites; it is this marked decrease in CQ accumulation that underlies the phenomenon of CQ resistance. CQ-R parasites can be partially resensitized to CQ in vitro by a range of weak bases, including the antihistamine chlorpheniramine and the calcium channel blocker verapamil.[196] This "resistance reversal" effect is characterized by both an increase in CQ accumulation and an increase in the CQ sensitivity of CQ-R parasites. However, the concentration of these reversal agents required to reverse CQ resistance is generally higher than that tolerated in vivo. The key molecular determinants of CQ resistance involve a number of mutations in the so-called CQ resistance transporter gene, or *pfcrt*. Of these, the predominant resistance-conferring mutation (K76T)[197] results in the loss of a positive charge from the putative substrate-binding site on the vacuolar side of the protein.[198] CQ-R *P. falciparum* is now found throughout the malaria-endemic world, with the exception of Central America and the Panama Canal. Of note, evidence indicates that the *pfcrt* mutation exerts a fitness cost on the malaria parasite. Twelve years after the drug was withdrawn from use in Malawi in 1993, a clinical trial undertaken in children in 2005 showed disappearance of the mutant *pfcrt* allele and return of CQ sensitivity.[199] The return of the *pfcrt* K76 CQ-sensitive allele has also been reported in other countries after withdrawal of CQ treatment, including Ethiopia, Tanzania, and Kenya.[200–202]

CQ-R *P. vivax* has developed more slowly than for *P. falciparum*. However, resistance has now been reported in nearly all countries where *P. vivax* is endemic. The geographic distribution of CQ-R *P. vivax* has been recently reviewed,[203] and a complete list of the clinical trials identified in this review is available online.[204] High rates of resistance are particularly notable in the island of New Guinea,[113,126] Indonesia,[205–207] Malaysian Borneo,[208] Cambodia,[129] Vietnam,[209] and Myanmar.[210] Resistance has been reported in India[211] and across countries in the Amazon basin, including Brazil,[212,213] Bolivia,[213] Peru,[214] Colombia,[215] and Guyana.[216] CQ-R *P. vivax* has also been reported in Turkey,[217] Ethiopia,[218,219] and Madagascar.[220]

The molecular mechanisms underlying CQ resistance in *P. vivax* remain uncertain. Although a possible role of orthologous genes in *P. vivax* are associated with resistance in *P. falciparum*, including *pvmdr1* and *pvcrt-o*, no specific genetic marker has been unequivocally demonstrated.[221]

If CQ is used for the treatment of *P. vivax*, close follow-up is essential to monitor for possible treatment failures, as previously unrecognized foci of CQ-resistant *P. vivax* are emerging. CQ should not be used to treat severe vivax malaria due to slower parasite clearance times compared with artemisinin derivatives.[222]

Toxicity

CQ is generally well tolerated.[60] The most commonly reported adverse effect is pruritus, which is more common in dark-skinned populations.[223] It predominantly affects the palms, soles, and scalp and starts within 24 hours of exposure and can last for several days. As systemic equilibration of CQ is relatively slow, this combined with the cardiac and central nervous system (CNS) toxicity of high plasma levels renders parenteral administration or overdose hazardous, with seizures and death from cardiovascular collapse resulting from high plasma levels.[224] Although CQ crosses the placenta,[225] doses used for chemoprophylaxis do not cause a significant increase in fetal abnormalities. CQ is safe for nursing mothers. When used for prolonged periods (>5 years prophylaxis), the cumulative accumulation can cause retinal damage,[226] and regular ophthalmologic examination is appropriate if long-term therapy is undertaken.

Quinine and Quinidine

Derived from the bark of the cinchona tree, quinine comprises a racemic mixture of D and L enantiomers. As the availability of quinine is reducing in the developed world, its D enantiomer, quinidine, which is also used as a cardiac antiarrhythmic, is increasingly being used as a replacement[227] (Fig. 41.7). IV quinine is the second-line alternative to IV artesunate for treatment of severe malaria.[227,228] Parenteral artesunate is more efficacious with a mortality benefit in severe malaria.[47,48] As is the case for CQ, the only life-cycle stage of *P. falciparum* that quinine is active

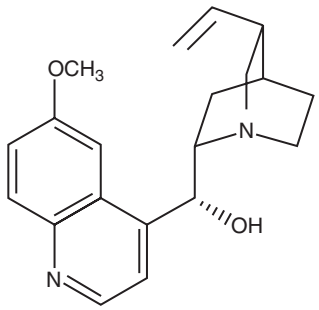

FIG. 41.7 Structure of quinine.

against is the asexual erythrocytic form. It has little effect on sporozoites or liver-stage parasites. It is gametocidal against *P. vivax* and *P. malariae* but not against *P. falciparum*. Quinine is active against the zoonotic primate malaria species *Plasmodium knowlesi.*[229] Although the mechanism of action of quinine against *Plasmodium* spp. is not known, it appears to inhibit the digestion of hemoglobin. It has also been shown to inhibit the adenosine triphosphatase of *P. falciparum* food vacuoles[230]; this mechanism appears to be independent of its alkalinization of the food vacuole.[231]

Pharmacokinetics

The pharmacokinetic properties of quinine have been extensively reviewed.[232] Two clinically important pharmacokinetic issues are the risk of underdosing in severe malaria, necessitating a loading dose (see later),[233] and the variation in pharmacokinetic parameters in patients with severe malaria.[232] Although quinine levels are higher in severe malaria, toxicity is uncommon compared with equivalent doses in healthy subjects. This is due to increased plasma binding to a1-acid glycoprotein, an acute-phase protein whose levels are elevated in acute malaria,[234] which results in a reduction of levels of free quinine by 25% to 30% in uncomplicated malaria and by 40% in severe malaria.[235–237] With increasing severity of malaria, there is also a reduction in the volume of distribution and clearance, particularly hepatic clearance, because of the changes in free quinine levels.[232] Both quinine and quinidine are metabolized by the hepatic microsomal enzyme cytochrome P-450 3A4; quinidine is also metabolized by CYP2D6.[232]

It is important to avoid confusion arising from calculation of the dose of quinine depending on its various salts. The following doses are equivalent: quinine base 100 mg; quinine sulphate 121 mg; quinine bisulphate 169 mg; and quinine dihydrochloride 122 mg. The dose of quinine sulfate for treatment of malaria is 10 mg salt/kg, given three times a day for 7 days.

Pharmacokinetic parameters of quinine in patients with acute renal failure appear to be similar to patients with severe malaria without renal failure.[238] A dose reduction of 30% to 50% is suggested only after 2 days of standard quinine therapy, including standard loading doses, for patients with acute renal failure or who remain severely unwell.[232]

Clinical Use

Quinine is less well tolerated than other antimalarials (see later) and requires prolonged course of treatment (at least 7 days) to effect a cure. Hence completion of a therapeutic course is problematic. It remains an option as second-line oral treatment of all species of malaria, particularly for pregnant women, infants, and patients with suspected drug-resistant infections recurring after a compromised treatment regimen. To reduce the risk of recrudescence, quinine (10 mg salt/kg q8h for 7 days) is often combined with clindamycin (10 mg/kg q12h for 7 days).[239] In patients older than 8 years, clindamycin can be substituted for either doxycycline (100 mg q12h in adults or 2.2 mg/kg q12h in children) or tetracycline (250 mg q6h in adults or 6 mg/kg q6h in children).[240] Further, because of the poor tolerability of quinine, especially after 3 days, many recommended oral regimens for mild malaria entail 3 days of quinine, with a full 7 days of the partner drug. When used for treatment of severe malaria, it is imperative that therapeutic drug concentrations are reached as quickly as possible. Hence an initial loading dose should be administered,[233] followed by a maintenance dose of 10 mg salt/kg q8h, starting 8 hours after the loading dose. Two loading-dose regimens can be used:

- The standard regimen is quinine dihydrochloride 20 mg of salt/kg by IV infusion over 4 hours. (Note: IV quinine is not available in the United States.)
- An alternative regimen has been suggested with quinine dihydrochloride 7 mg of salt/kg by IV infusion over 30 minutes, followed by 10 mg/kg infused over 4 hours.[241]

A common clinical dilemma is whether to administer a loading dose if there is a history of self-medication with antimalarials. The risk of inadequate treatment due to underdosing must be weighed against the risk of serious cardiac toxicity due to overdose. Authorities suggest omitting the loading dose if more than 2 g of quinine has been administered within the past 48 hours.[242,243]

If an IV infusion cannot be safely administered, quinine can also be administered intramuscularly. Although pharmacokinetic studies of IM quinine are lacking in adult patients with severe malaria, a loading dose appears to be well absorbed in patients with uncomplicated malaria[244] and efficacious in severe malaria.[245] Quinine should be diluted with water to reach a concentration for administration of less than 150 mg/mL to reduce local pain and improve absorption, and be administered in divided doses into each thigh.[232,246]

Quinine Resistance

Quinine resistance in *P. falciparum* was first reported in Brazil in 1908.[247] Although quinine resistance of *P. falciparum* varies globally, published data on its prevalence since the increased use of artemisinin antimalarials are sparse. Resistance is more common and severe in Southeast Asia and has paralleled the rise of resistance to mefloquine,[248] suggesting cross-resistance between these two drugs. As is the case for mefloquine, amplification of the drug transporter *pfmdr1* is associated with resistance. However, there is a paucity of data associating *pfmdr1* amplification and clinical outcome.[249] Genetic markers of quinine resistance have been reviewed.[250]

Quinine for Treatment of Babesiosis

Quinine in combination with clindamycin has been the treatment of choice for severe babesiosis at doses similar to those used for treatment of malaria: quinine 8 mg salt/kg (up to 650 mg in adults) every 8 hours, with clindamycin 7 to 10 mg/kg (up to 600 mg in adults) every 6 to 8 hours.[251] Azithromycin with atovaquone is a better-tolerated regimen and equally effective in patients with mild-moderate babesiosis.[252]

Toxicity

The syndrome of cinchonism (tinnitus, high-tone deafness, visual disturbances, headache, dysphoria, vomiting, and postural hypotension) commonly occurs at therapeutic plasma levels, with plasma levels correlating with severity.[253] Reversible deafness, which is predominantly high-tone, also correlates with plasma concentrations.[254–257] The most common cardiovascular adverse events associated with quinine and quinidine are postural hypotension and syncope.[74] Although cardiotoxicity due to quinine is unusual at plasma concentrations in the therapeutic range,[254,258] quinidine causes QT interval prolongation in approximately 3% of patients.[259] Fatal ventricular arrhythmias have only been described in a patient with a preexisting prolonged QT interval (490 ms).[260] Acute toxicity caused by inadvertent rapid infusion may cause life-threatening cardiac arrhythmias, including ventricular tachycardia and ventricular fibrillation.[261] Patients being treated with quinidine should have regular clinical assessment for hypotension, a baseline electrocardiogram for assessment of corrected QT interval, and cardiac monitoring. Patients being treated with quinine do not generally require cardiac monitoring unless there is preexisting heart disease or the potential of interactions with other medications that are known to affect cardiac electrophysiology, or in children younger than 2 years receiving IV treatment. Quinine has been associated with transient retinal toxicity, which typically occurs in drug overdose; the majority of patients report complete blindness, but alterations in color vision, blurring of vision, or visual field restriction are described.[262]

An important adverse effect of quinine treatment in severe malaria is hypoglycemia.[263,264] Pregnant women are particularly susceptible to this complication.[265] All patients receiving quinine or quinidine should be monitored for hypoglycemia, and any deterioration in clinical status (including seizures or altered mental status) should prompt assessment of plasma glucose. Patients receiving IV therapy should also receive an IV infusion of dextrose.

Blackwater fever is the syndrome of massive hemolysis (with visible hemoglobinuria) in the setting of severe malaria, glucose-6-phosphate dehydrogenase deficiency (G6PDd), and quinine treatment. Because malaria is also associated with hemolysis, the relative roles of quinine and G6PD are unclear.[245,266,267]

Allergic reactions, such as drug-induced thrombocytopenia,[268] hepatitis, urticaria, and other more severe dermatologic phenomena (erythema multiforme, fixed-drug eruptions, and toxic epidermal

necrolysis),[261,269,270] are all much less common after malaria chemotherapy than when the drug has been used long term.

The risks of using quinine in pregnancy must be weighed against the known deleterious effects of malaria on pregnancy. Some, but not all, animal studies have demonstrated abnormalities of the inner ear, auditory nerve, and CNS.[186,271–273] At standard doses, quinine does not increase the rate of spontaneous abortion, and its use in the first trimester does not appear to be associated with birth defects.[274] Controlled trials have not found evidence of an increased risk of birth defects.[275] As noted earlier, in pregnant women with severe malaria, hypoglycemia appears to be a common complication of quinine treatment.[276]

8-AMINOQUINOLINES

Primaquine

Primaquine (Fig. 41.8) is the most widely used 8-aminoquinoline antimalarial compound. Drugs in this class are unique in having activity against asexual, sexual, and liver stages of the parasite.[277] Although discovered almost 80 years ago and recommended by most national and international malaria treatment guidelines, primaquine is often underused owing to fear regarding its toxicity and uncertainty regarding the efficacy. This is especially the case in settings where G6PD testing (see later) is not readily available. However, there has been a resurgent interest in this drug and its role in interrupting malaria transmission, achieving the radical cure of *P. vivax,* and reducing the spread of drug resistance.[278]

The mechanism of action of the 8-aminoquinolines is unknown but hypothesized to be due to oxidative metabolites that affect parasite pyrimidine synthesis and disrupt the mitochondrial electron transport chain.

Pharmacokinetics

Primaquine is essentially a prodrug that is extensively and rapidly metabolized, with only a small fraction of the parent drug excreted unchanged. Little is known of the pharmacokinetics of the metabolites that are responsible for both its antimalarial activity and toxicity. Its principal metabolite, carboxyprimaquine, is formed as a result of oxidative deamination, which is thought to involve both the cytochrome-P450 enzyme complex and monoaminooxidases.[279] Primaquine is rapidly and almost completely absorbed after oral administration, with C_{max} of about 3 hours. It is cleared by hepatic biotransformation, with an elimination half-life of 8 hours. Repeated dosing does not alter its pharmacokinetic profile.[280] Although there are no pharmacokinetic studies of the enantiomers in humans, animal studies point to stereoselective metabolism of positive (+) and negative (–) primaquine,[281] with the (+) enantiomer exhibiting a significantly longer elimination half-life.[282] These studies also suggest a difference in toxicity between the two enantiomers that may be relevant to humans. Recent data indicate that the activity of primaquine is dependent on its metabolism by the cytochrome P-450 CYP2D6 metabolic pathway, and that slow metabolism may explain drug failure in some situations.[283]

Clinical Use

Primaquine has three main clinical applications: the radical cure of *P. vivax* and *P. ovale* infection, causal prophylaxis, and the reduction of *P. falciparum* transmission. The dose of primaquine is expressed as the amount of base. There is only one salt, the diphosphate, available for use. A dose of 15 mg primaquine base is equivalent to approximately 26.3 mg primaquine diphosphate salt.

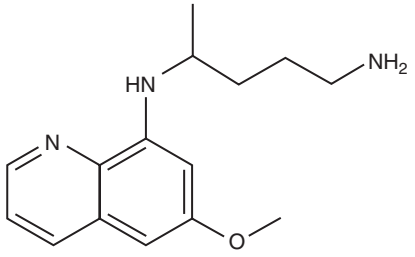

FIG. 41.8 Structure of primaquine.

Radical Cure

Primaquine and now tafenoquine are the two licensed agents for the radical cure of *P. vivax* and *P. ovale.* Despite more than 60 years of continuous use, there is still neither evidence nor consensus on the optimal dose or dosing regimen.[284] The main determinant of primaquine antirelapse efficacy is the total dose of primaquine administered, rather than the dosing schedule.[277] WHO guidelines for the radical cure of vivax malaria currently recommend the use of a daily dose of 0.25 mg/kg per day of primaquine base for 14 days (3.5 mg/kg total dose) taken with food once daily, coadministered with CQ or ACT depending on CQ sensitivity in the region.[35,285] However, this standard dose regimen of primaquine fails to prevent relapses in many different endemic locations.[284] High rates of recurrence can be overcome by administering a higher total dose (7 mg/kg, equivalent to an adult dose of 30 mg/day for 14 days), a regimen that is now recommended for Southeast Asia and Oceania. However, in practice most national guidelines still recommend lower doses. To reduce the risk of hemolysis and improve tolerability from GI disturbance, the target cumulative dose of primaquine is recommended to be administered over 14 days, either as a once- or twice-daily regimen. Advocating such prolonged courses of treatment can result in significant problems with adherence.[286] Short-course, high-dose regimens have the potential to increase patient adherence and thus effectiveness,[287] but appropriately powered prospective multicentered, randomized, controlled trials are necessary.

Primaquine can induce hemolysis in patients with G6PDd. In patients with mild G6PDd, primaquine 45 to 60 mg once weekly for 8 weeks may be better tolerated.[288] In some patients, particularly those who have previously suffered severe adverse effects of primaquine, it may be prudent to withhold primaquine treatment and instead promptly treat relapses. Primaquine use is contraindicated in pregnancy because the G6PD status of the fetus is unknown, and even in normal individuals, fetal red cells are relatively deficient in G6PD. Instead, after treatment of *P. vivax* or *P. ovale* infection, a pregnant woman should take weekly CQ prophylaxis until after delivery, when hypnozoite eradication can be considered. Treatment is contraindicated in breastfeeding women, due to concerns of excretion of primaquine in breast milk. Data on the administration of primaquine to children are limited, although the current WHO guidelines recommend administration to children older than 6 months. The dose is the same as for adults adjusted for body weight.

Reduction of Transmission

Interrupting transmission has become a priority of many malaria control programs now set on achieving malaria elimination. The use of primaquine as a gametocytocidal drug in areas of low malaria transmission has potential to reduce the incidence of infection and retard the spread of drug-resistant parasites. The addition of primaquine to current ACTs reduces gametocyte carriage after ACT administration.[289] Current WHO guidelines recommend a single dose of 0.25 mg/kg at the start of schizonticidal treatment.[35]

Chemoprophylaxis

The activity of primaquine activity against all species of plasmodia makes it a useful agent for prophylaxis. For this indication, a daily dose of 0.5 mg/kg (equivalent to an adult dose of 30 mg base) is well tolerated and effective. It is particularly useful in areas where the risk of *P. vivax* infection is high.[290] When used for primary prophylaxis, it should be taken daily for 1 to 2 days before travel to malarious areas, daily while in the areas, and daily for 7 days after leaving the areas. Primary prophylaxis with primaquine obviates the need for presumptive antirelapse therapy where travel has been to a region of high risk for *P. vivax* infection. If primaquine is used for this purpose, G6PDd must be excluded in advance.

Toxicity

Although primaquine is generally well tolerated, its propensity to cause GI adverse effects and hemolysis warrants caution. Nausea, headache, vomiting, and abdominal pain are relatively common, particularly when doses exceed 30 mg (0.5 mg/kg). These adverse effects can be reduced substantially by taking the drug with food. Diarrhea, weakness, visual disturbance, and pruritus occasionally occur.

Primaquine can induce significant hemolysis, particularly in those with G6PDd.[291] G6PDd is the most common heritable enzymopathy in the world, with a prevalence ranging from 2% to 40%.[292] The gene encoding G6PD is found on the X chromosome, and inheritance is thus sex linked. Individuals with less than 10% of normal enzyme activity are at risk of life-threatening hemolysis,[293] whereas those with milder variants may suffer negligible effects.[277] Primaquine-induced hemolysis is dose dependent, the dose-effect relationship depending on the degree of G6PDd, which is graded according to the level of enzyme activity. This is particularly important in poorly resourced settings where routine G6PD testing is not available. In these circumstances health care providers simply omit radical cure or prescribe lower and prolonged courses and stop treatment in the event of frank hematuria or overt hemolysis.

Primaquine metabolites induce the oxidation of hemoglobin into methemoglobin, a process that is dose dependent and occurs in normal and G6PDd erythrocytes. In most treatment regimens methemoglobin concentrations induced by primaquine are asymptomatic, transient, and rarely apparent. However, prolonged administration of 45 mg (0.75 mg/kg) weekly or 15 mg (0.25 mg/kg) daily may increase methemoglobin levels to more than 30% in some individuals.[294] Individuals with a genetic polymorphism resulting in reduced nicotinamide adenine dinucleotide cytochrome b5 reductase activity are particularly vulnerable to this effect. Quinine appears to offer some protection against methemoglobinemia, whereas combination with CQ can result in methemoglobin levels fourfold higher in healthy subjects.[295]

Primaquine exerts other hematologic side effects, such as mild leukocytosis and leukopenia (specifically granulocytopenia) within several days of starting treatment. It has also been associated with arrhythmias, although these are only induced at supratherapeutic doses.

Tafenoquine

Tafenoquine is an 8-aminoquinoline antimalarial drug developed by the Walter Reed Army Institute of Research (WRAIR) and GlaxoSmithKline Pharmaceuticals (GSK). Like primaquine, it is active against all forms of malaria. Tafenoquine has similar antimalarial properties as primaquine. Because of tafenoquine's long half-life, the radical cure of *P. vivax* can be achieved with a single dose. Tafenoquine can also be administered intermittently for chemoprophylaxis and clearance of circulating gametocytes.

Tafenoquine is approximately 10 times more potent than primaquine against liver-stage hypnozoites in rhesus monkeys. Unlike primaquine, tafenoquine inhibits heme polymerization similar to the 4-aminoquinolines, an effect that may explain its activity against the asexual intraerythrocytic stages of both *P. falciparum* and *P. vivax*.[296] Tafenoquine has additional antiparasitic activity in mosquitoes, preventing sporozoite development in the mosquito.[297,298]

Pharmacokinetics

Tafenoquine is rapidly absorbed; Absorption is increased when taken with food, which also reduces the severity of GI adverse effects.[299] It has a large volume of distribution and a prolonged elimination half-life (≈16 days),[300] thus offering the potential of a longer dosing interval for prophylaxis compared with primaquine. Unlike primaquine, tafenoquine accumulates in erythrocytes, which may contribute to its greater potency compared with primaquine.[301] Like primaquine, the activity of tafenoquine may require CYP2D6 metabolism.[302]

Clinical Use

Tafenoquine is formulated as the succinate salt, with 250 mg of salt equal to 200 mg base. It is marketed as 100- and 150-mg tablets of tafenoquine base. The prophylactic activity of tafenoquine against *P. falciparum* in a variety of weekly regimens varied from 86% to 89%, rising to 95% against *P. vivax*.[303,304] Against *P. vivax* hypnozoites, a single-dose regimen achieves reliable radical cure.[304,305a,305b] A multicentered phase III clinical trial has been completed and showed that a 300-mg dose of tafenoquine was not inferior to a 14-day primaquine regimen (total dose 3.5 mg/kg). The US Food and Drug Administration approved tafenoquine for single-dose radical cure of *P. vivax* malaria in adults in July 2018. Prophylaxis was later approved for adults at a dose of 200 mg once per day for 3 days within 1 week of travel, 200 mg once per week during travel, and 200 mg once within a week after completing travel. The ability of tafenoquine to kill parasites in the mosquito suggests that it may be useful during malaria epidemics by blocking transmission.[298]

Toxicity

The most frequently noted adverse events are mild GI upset, headaches, and myalgia. As with primaquine, the main concern is that of hemolysis in persons with G6PDd, particularly if tafenoquine's slow elimination results in sustained toxicity.[306] Therefore G6PD status should be checked before administering the drug. In view of the lack of data of safety in heterozygote females with intermediate deficiency, the manufacturer recommends that patients should have a G6PD enzyme activity greater than 70%; this currently requires confirmation by spectrophotometry. Tafenoquine should not be used in pregnant women or in lactating mothers with infants of deficient or unknown G6PD status. Tafenoquine at prophylaxis doses is not recommended in those with psychotic disorders. Methemoglobinemia may be observed, as with primaquine.

Atovaquone

Originally developed as an antimalarial agent on the basis of potent in vitro activity against drug-resistant strains of *P. falciparum*,[307] the hydroxynaphthoquinone atovaquone (Fig. 41.9) has subsequently found to be active against a number of other microorganisms, including *Pneumocystis jirovecii*,[308] *Toxoplasma gondii*,[309] *Babesia microti, Cryptosporidium parvum, Encephalitozoon intestinalis, Leishmania donovani, Entamoeba histolytica,* and *Trichomonas vaginalis*. Toxoplasmosis and babesiosis can be effectively treated with atovaquone, when used in combination with pyrimethamine and azithromycin, respectively.

Studies on the potentiation of atovaquone by other antimalarial drugs revealed evidence of synergistic activity with proguanil.[310] After clinical trials, this culminated in the development of a fixed-dose combination (Malarone) for the treatment and prevention of malaria.[311,312] Although atovaquone is active against both the erythrocytic and preerythrocytic (liver) stages of *Plasmodium* spp., it does not eradicate hypnozoites from the liver, so patients with *P. vivax* or *P. ovale* infections require radical cure with an 8-aminoquinoline.

Atovaquone inhibits the electron transport system at the cytochrome bc1 complex.[313] There is obligatory coupling of pyrimidine biosynthesis and electron transport via ubiquinone/ubiquinol. Selectivity is achieved through the difference between mammalian and plasmodial electron transport systems in their sensitivity to the hydroxynaphthoquinones. In addition, plasmodia depend completely on pyrimidine synthesis, whereas mammalian cells use a pyrimidine salvage pathway. The mechanism of potentiation of atovaquone by proguanil appears to be related to proguanil itself; metabolism to cycloguanide is not required.[314]

Pharmacokinetics

Atovaquone is highly lipophilic and shows significant variation in oral bioavailability. After a single oral dose, absorption is slow, increasing twofold to threefold with a fatty meal, and is dose limited above 750 mg.[307] It is highly protein bound (>99.9%).[315] The liver is the main route of elimination, with enterohepatic circulation contributing to its prolonged

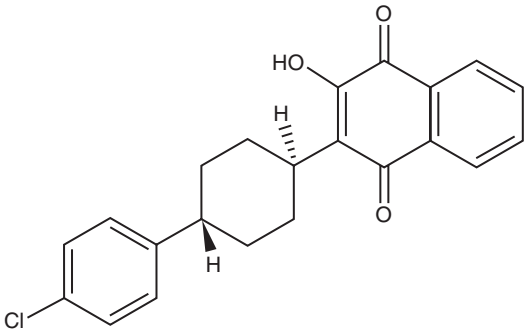

FIG. 41.9 Structure of atovaquone.

half-life. Negligible biotransformation occurs in vivo with atovaquone being eventually eliminated in the feces, with less than 1% excreted in the urine. Its elimination half-life is increased in patients with moderate hepatic impairment, probably due to impaired enterohepatic circulation. Caution is advised in patients with hepatic dysfunction. Because urinary excretion is negligible, no dosage adjustment is necessary in patients with renal impairment. However, because proguanil and its metabolite cycloguanil are primarily excreted in the urine, use of the atovaquone-proguanil combination (Malarone) is contraindicated in patients with creatinine clearance of less than 30 mL/min. Atovaquone is not teratogenic and does not cause reproductive toxicity in rats at plasma concentrations of up to two to three times human levels.

Clinical Use

Atovaquone-proguanil (Malarone), administered as a single tablet daily (250/100 mg), is a highly effective chemoprophylactic regimen. Its major drawback is the cost of the medication due to the high cost of synthesis of atovaquone. It is also an effective treatment for all species of human malaria (in a dose of four tablets daily for 3 days in adults; in children use a weight-based dose of the pediatric formulation: 62.5 mg atovaquone/25 mg proguanil), including drug-resistant strains of *P. falciparum*. However, for the latter it is probably safer to combine it with an artemisinin drug. Of interest, clinical trials have shown that a full treatment course (4 tablets daily for 3 days) of atovaquone-proguanil results in protection from reinfection with *P. falciparum* for 28 to 32 days,[316–319] and a recently undertaken clinical trial showed that a single dose of atovaquone-proguanil results in prophylaxis of sufficient duration to suggest that a weekly dosing schedule may be sufficient. The study also supported previous data indicating activity against incubating liver-stage parasites.[320]

Resistance

Reports of clinical strains of *P. falciparum* resistant to atovaquone-proguanil typically involve changes at codon 268[308] of the cytochrome b gene.[321] Although there have been reports of prophylaxis failure in patients taking atovaquone-proguanil, these have been associated with subtherapeutic drug levels that have permitted the in vivo evolution of drug-resistant parasites.[322] Of note, it appears that even if atovaquone resistance emerges in vivo, it is unlikely to be transmissible through the mosquito due to the requirement for wild-type cytochrome C enzyme in the mosquito vector.[323] Mutations in the cytochrome b gene occur more commonly in patients with *P. jirovecii* infection in the acquired immunodeficiency syndrome (AIDS) after treatment with atovaquone, but its clinical significance is unknown.[324] Phenotypic resistance to atovaquone has not been demonstrated for *P. jirovecii*. Atovaquone-resistant isolates of *T. gondii* also demonstrate mutations in the cytochrome b gene.[325] Clinical failures of azithromycin-atovaquone therapy for babesiosis in immunocompromised patients have been reported.[326]

Toxicity

Atovaquone is generally well tolerated, but reported adverse events include nausea, vomiting, diarrhea, headache, fever, and transient elevations in liver function tests. Caution should be used when administering atovaquone concurrently with other highly plasma protein–bound drugs with narrow therapeutic indices because competition for binding may occur. Coadministration of rifampin results in significant reductions in atovaquone plasma concentrations. Tetracycline and metoclopramide reduce atovaquone plasma concentrations by 40% and 50%, respectively. Atovaquone increases plasma concentrations of zidovudine by approximately 33% due to inhibition of hepatic glucuronidation. Clinically insignificant reductions in both trimethoprim and sulfamethoxazole occur with atovaquone.[327]

Folate Antagonists

This class of drugs has been used for both prophylaxis and treatment of malaria. In view of their ability to act synergistically, they are often used in combination. However, the efficacy and therefore use of the antifolates have fallen due to the development of high-grade resistance. Activity of the antifolates derives from selective inhibition of parasite rather than host enzymes responsible for one-carbon metabolism.

DIHYDROFOLATE REDUCTASE INHIBITORS

Unlike mammalian cells, *P. jirovecii* and protozoan parasites cannot use preformed pyrimidines obtained through salvage pathways but rely completely on de novo pyrimidine synthesis, for which folate derivatives are essential cofactors. This process, thymidine synthesis, is dependent on the enzyme dihydrofolate reductase (DHFR). DHFR inhibitors compete with the substrate, dihydrofolate, by binding reversibly to the active site of DHFR. Although DHFR is found in almost all organisms, the amino-acid sequence of DHFR varies between species, thus explaining the selective action of different DHFR inhibitors.[328]

Proguanil (Chloroguanide)

Although proguanil (Fig. 41.10) is an effective schizonticide, its onset of action is too slow to recommend its use alone for malaria treatment. Proguanil is now almost exclusively used with atovaquone for malaria chemoprophylaxis, and for the oral treatment of uncomplicated malaria. It exerts its antimalarial activity primarily through its metabolites cycloguanil and 4-chlorophenyl biguanide, which inhibit dihydrofolate reductase in the parasite and disrupt deoxythymidylate synthesis, thus interfering with the biosynthesis of pyrimidines required for nucleic acid replication. Proguanil also exhibits intrinsic activity, possibly involving mitochondrial toxicity, that is synergistic in combination with atovaquone.[314] This is further suggested by the finding that cycloguanil-resistant parasites retain their sensitivity to high concentrations of proguanil.[329] In addition, a *P. falciparum* strain transfected with a variant form of human dihydrofolate reductase selectable by methotrexate had increased resistance to cycloguanil but remained susceptible to proguanil.[330]

Pharmacokinetics

Proguanil is extensively absorbed in the fasting or fed state, with peak plasma levels occurring 1 to 6 hours after a single dose. The drug is 75% protein bound; this appears to be unaffected by the concentration of atovaquone. Metabolism of proguanil to cycloguanil is mediated in the liver by cytochromes 3A4 and 2C19.[331] Genetic polymorphism of CYP2C19 leads to a bimodal distribution of proguanil and cycloguanil concentrations in humans. Therefore markedly lower cycloguanil and moderately higher proguanil plasma concentrations occur in poor metabolizers (18%–25% in Asians and Africans; 3% in Caucasians[332]). However, this does not appear to affect therapeutic response.[312] The main routes of elimination are hepatic biotransformation and renal excretion, with 40% of proguanil and 20% of its metabolites excreted in the urine. Patients with renal failure may develop hematologic toxicity due to accumulation of the drug. Drug levels are increased and elimination is impaired in patients with hepatic impairment. There are no clinical data indicating that folate supplementation diminishes drug efficacy; women of childbearing age for whom atovaquone-proguanil

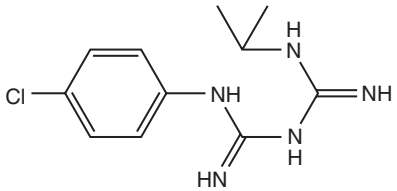

FIG. 41.10 Structure of proguanil.

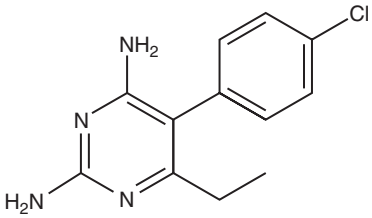

FIG. 41.11 Structure of pyrimethamine.

is prescribed should continue taking folate supplements to prevent neural-tube birth defects. Symptomatic adverse effects are dose related and include mouth ulcers, dyspepsia, and hair loss. Idiosyncratic reactions are rare. No significant clinical drug interactions have been reported.

Pyrimethamine

Pyrimethamine (Fig. 41.11) in combination with short-acting sulfonamides is effective in malaria, toxoplasmosis, and isosporiasis. Drug resistance to pyrimethamine due to mutations in DHFR is an important problem in treatment of *P. falciparum* and *P. vivax*. Pyrimethamine is always used in combination with either a sulfonamide or dapsone.

Pharmacokinetics

Pyrimethamine is well absorbed after oral administration to healthy volunteers, patients with malaria, and in AIDS patients with cerebral toxoplasmosis. Pyrimethamine is about 90% bound to plasma proteins, principally albumin, but this varies with drug concentration; the unbound fraction increases concomitantly with drug concentrations. In healthy volunteers, drug concentration remains at therapeutic levels for up to 2 weeks; drug levels are lower in patients with malaria. In infants with congenital toxoplasmosis, cerebrospinal fluid drug concentrations reach 10% to 25% of serum concentrations.[333] The high lipid solubility of pyrimethamine suggests that it probably crosses the placenta readily, but no data are available. Pyrimethamine is excreted into breast milk, but its concentration appears too low to cause dose-related adverse effects.[334] Pyrimethamine clearance is not reduced by renal disease, but caution is advised in both kidney and liver disease.

Toxicity

Adverse effects are common but rarely serious. In children toxicity is frequently seen with doses greater than 25 mg. Concentration-dependent suppression of marrow function occurs at the higher doses used for toxoplasmosis; at these doses the drug should be administered with folinic acid. Prolonged use and folate deficiency put patients at significant risk for marrow toxicity, glossitis, stomatitis, and exfoliative dermatitis. Rarely, a photosensitive rash can develop; it regresses after treatment stops.[335] When combined with dapsone, agranulocytosis can develop but usually only when the maximum dose is exceeded.[336] When combined with sulfadoxine, severe skin reactions can occur rarely but are probably attributable to the sulfa component. Severe idiosyncratic reactions to pyrimethamine are rare. The synergy of pyrimethamine and sulfadiazine against *T. gondii* may be reversed by zidovudine.[337]

Trimethoprim

For a discussion of trimethoprim, see Chapter 34.

DIHYDROPTEROATE SYNTHETASE INHIBITORS

Unlike multicellular eukaryotes, many unicellular organisms synthesize folate rather than relying on dietary sources of this cofactor. The sulfonamides and sulfones inhibit the enzymatic activity of a key enzyme in the folate synthesis pathway, dihydropteroate synthetase (DHPS). DHPS catalyzes the conversion of para-aminobenzoate to dihydropteroate.

Sulfonamides

Sulfonamides are synthetic drugs with low potency against a wide range of protozoa. No drug of the group is potent enough to have therapeutic activity when used alone for these infections; all are given in synergistic combination with a DHFR-inhibitor such as pyrimethamine or trimethoprim.

Sulfadiazine and Sulfamethoxazole

For a discussion of sulfadiazine and sulfamethoxazole, see Chapter 34.

Sulfadoxine

Sulfadoxine is available as an oral formulation with pyrimethamine.

Pharmacokinetics

When a single oral dose is given to healthy patients, it is rapidly and extensively absorbed from the gut, reaching C_{max} within 4 hours. The C_{max} in healthy patients is about 55% that of nonimmune adults with falciparum malaria. Sulfadoxine is about 94% bound to plasma proteins. It appears to concentrate within malaria-infected erythrocytes and crosses the blood-brain barrier, achieving 30% to 60% of the plasma concentration. The majority of sulfadoxine undergoes glomerular filtration unchanged; however, of the filtered drug, about 70% undergoes tubular resorption. Sulfadoxine is excreted in the bile, but the majority is reabsorbed from the gut. Weekly dosing results in steady-state concentration after seven doses.

Toxicity

The adverse effects of sulfonamides are best considered together; distinctions between drugs typically result from differences in elimination. The most common adverse effects include fever; arthralgias; marrow suppression; rash, including Stevens-Johnson syndrome; methemoglobinemia; and hemolysis in patients with G6PDd. At high doses and in patients with volume depletion, sulfonamides may crystallize in acidic urine, leading to tubular damage and severe renal insufficiency.

Sulfonamides typically cause adverse drug interactions by displacement of a drug from plasma protein binding sites, inhibition of biotransformation, and increasing the pharmacodynamic response. Sulfonamides potentiate the effects of warfarin, sulfonylureas, phenytoin, and other drugs with a narrow therapeutic range through the first two mechanisms.

Sulfones

Dapsone is the only member of this group in regular clinical use. It is active against *P. falciparum, T. gondii,* and *P. jirovecii,* but its potency is limited, and treatment of these pathogens requires combination with a DHFR inhibitor. For a detailed discussion of sulfones, see Chapter 39.

Dapsone is slowly absorbed, with an absorption half-life of 1 hour in healthy subjects; it is more slowly absorbed in children with uncomplicated malaria.[338] Dapsone is extensively metabolized by acetylation, hydroxylation, and conjugation with glucuronic acid to a variety of inactive metabolites. The parent drug and these metabolites are mainly excreted in the bile, and there is significant enterohepatic circulation. The half-life of dapsone is about 30 hours in healthy subjects and young children with malaria.

Agranulocytosis has been commonly reported among individuals taking dapsone with pyrimethamine for malaria prophylaxis. The estimated prevalence of this reaction is 1:2000 to 1:5000 prescriptions. For this reason, this combination was removed from recommendations for malaria chemoprophylaxis. The mechanism of this was unclear but presumed to be due to the dapsone component.

ANTIBIOTICS WITH ANTIMALARIAL ACTIVITY

Doxycycline and Tetracycline

Both doxycycline and tetracycline are important antimalarial agents. For details of their pharmacokinetic properties and adverse effects, see Chapter 26. Neither agent acts rapidly enough to be used alone in patients with acute falciparum malaria. The slow action of these and other antibiotics discussed later is due to the fact that the drugs target the translational machinery of the plastid organelle of the parasite,[339] and therefore a lag of one parasite life cycle is required before antiparasitic activity is apparent. However, both agents are useful as follow-on agents after initial treatment with quinine or artesunate to prevent recrudescence of parasitemia. Daily doxycycline is a preferred prophylactic regimen for malaria.

MACROLIDES

Azithromycin

Azithromycin, a macrolide, has activity against several protozoa. For a detailed discussion of its pharmacokinetics and adverse effects, see Chapter 29. It is an effective treatment of babesiosis when combined with atovaquone.[252] This combination is better tolerated than quinine

and clindamycin as a treatment for this infection. Azithromycin has been used with pyrimethamine to treat patients infected with *T. gondii*, but relapse rates were unacceptably high with maintenance doses used for suppression.[340,341] It may be useful as alternative therapy for ocular toxoplasmosis.[342] Although azithromycin has activity against *Plasmodium* spp., it is not sufficiently potent to be used for prophylaxis or treatment of *P. falciparum*.[343,344] However, it may be efficacious in preventing *P. vivax* infection.[345] Although it has been studied as a partner drug for artemisinins, results of clinical trials do not support a role for this drug in ACT. The drug is under active investigation as an option for intermittent preventive therapy of malaria in pregnancy.

Clindamycin

Clindamycin shows useful activity against several protozoa. Its pharmacokinetics are discussed in Chapter 29. It has been used with quinine for the treatment of CQ-R falciparum malaria; this regimen is the preferred one for treatment of malaria in the first trimester of pregnancy and as a second-line treatment in the second and third trimesters. It is also an option for the oral phase of treatment for severe malaria and is the treatment of choice for severe babesiosis.[346] The combination of clindamycin with artesunate rather than with quinine leads to faster parasite clearance and equivalent cure rates.[347] The major adverse effect of clindamycin is the development of pseudomembranous colitis.

Key References

The complete reference list is available online at Expert Consult.

6. Phyo AP, et al. Antimalarial activity of artefenomel (OZ439), a novel synthetic antimalarial endoperoxide, in patients with *Plasmodium falciparum* and *Plasmodium vivax* malaria: an open-label phase 2 trial. *Lancet Infect Dis*. 2016;16:61–69.
17. Batty KT, et al. A pharmacokinetic and pharmacodynamic study of intravenous vs oral artesunate in uncomplicated falciparum malaria. *Br J Clin Pharmacol*. 1998;45:123–129.
26. McGready R, et al. Pharmacokinetics of dihydroartemisinin following oral artesunate treatment of pregnant women with acute uncomplicated falciparum malaria. *Eur J Clin Pharmacol*. 2006;62:367–371.
35. World Health Organization. *Guidelines for the Treatment of Malaria*. Third ed. Geneva: World Health Organization; 2015.
37. Simpson JA, et al. Population pharmacokinetics of mefloquine in patients with acute falciparum malaria. *Clin Pharmacol Ther*. 1999;66:472–484.
38. White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B Biol Sci*. 1999;354:739–749.
39. Carrara VI, Zwang J, Ashley EA, et al. Changes in the treatment responses to artesunate-mefloquine on the northwestern border of Thailand during 13 years of continuous deployment. *PLoS ONE*. 2009;4:e4551.
40. Charle P, et al. Artesunate/amodiaquine malaria treatment for Equatorial Guinea (Central Africa). *Am J Trop Med Hyg*. 2013;88:1087–1092.
44. Price RN, et al. Effects of artemisinin derivatives on malaria transmissibility. *Lancet*. 1996;347:1654–1658.
47. Dondorp A, et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. 2005;366:717–725.
48. Dondorp AM, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*. 2010;376:1647–1657.
49. Karunajeewa HA, et al. Rectal administration of artemisinin derivatives for the treatment of malaria. *JAMA*. 2007;297:2381–2390.
54. Ashley EA, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*. 2014;371:411–423.
56. Ariey F, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. *Nature*. 2014;505:50–55.
57. Tun KM, et al. Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker. *Lancet Infect Dis*. 2015;15:415–421.
60. Taylor WR, White NJ. Antimalarial drug toxicity: a review. *Drug Saf*. 2004;27:25–61.
71. Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial agents. Fact or fiction? *Drug Saf*. 1995;12:370–383.
74. Chan XHS, et al. Risk of sudden unexplained death after use of dihydroartemisinin-piperaquine for malaria: a systematic review and Bayesian meta-analysis. *Lancet Infect Dis*. 2018;18:913–923.
75. Rolling T, et al. Delayed hemolysis after treatment with parenteral artesunate in African children with severe malaria—a double-center prospective study. *J Infect Dis*. 2014;209:1921–1928.
77. Jaureguiberry S, et al. Postartesunate delayed hemolysis is a predictable event related to the lifesaving effect of artemisinins. *Blood*. 2014;124:167–175.
80. McGready R, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. *Clin Infect Dis*. 2001;33:2009–2016.
84. Manyando C, et al. A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated *Plasmodium falciparum* malaria during pregnancy. *Malar J*. 2012;11:141.
85. Moore KA, et al. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. *Lancet Infect Dis*. 2016;16:576–583.
91. Price RN, et al. Molecular and pharmacological determinants of the therapeutic response to artemether-lumefantrine in multidrug-resistant *Plasmodium falciparum* malaria. *Clin Infect Dis*. 2006;42:1570–1577.
94. Abdulla S, et al. Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. *Lancet*. 2008;372:1819–1827.
95. Worldwide Antimalarial Resistance Network (WWARN) AL Dose Impact Study Group. The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data. *Lancet Infect Dis*. 2015;15:692–702.
98. Price RN, et al. Mefloquine resistance in *Plasmodium falciparum* and increased *pfmdr1* gene copy number. *Lancet*. 2004;364:438–447.
104. Piola P, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. *Lancet Infect Dis*. 2010;10:762–769.
106. McGready R, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated *Plasmodium falciparum* treatment in pregnancy. *PLoS Med*. 2008;5:e253.
107. PREGACT Study Group, et al. Four artemisinin-based treatments in African pregnant women with malaria. *N Engl J Med*. 2016;374:913–927.
117. WorldWide Antimalarial Resistance Network (WWARN) DP Study Group. The effect of dosing regimens on the antimalarial efficacy of dihydroartemisinin-piperaquine: a pooled analysis of individual patient data. *PLoS Med*. 2013;10:e1001564. discussion e1001564.
122. Karunajeewa HA, et al. A trial of combination antimalarial therapies in children from Papua New Guinea. *N Engl J Med*. 2008;359:2545–2557.
126. Ratcliff A, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. *Lancet*. 2007;369:757–765.
130. Amato R, et al. Genetic markers associated with dihydroartemisinin-piperaquine failure in *Plasmodium falciparum* malaria in Cambodia: a genotype-phenotype association study. *Lancet Infect Dis*. 2017;17:164–173.
131. Witkowski B, et al. A surrogate marker of piperaquine-resistant *Plasmodium falciparum* malaria: a phenotype-genotype association study. *Lancet Infect Dis*. 2017;17:174–183.
147. Ringwald P, Bickii J, Basco LK. Efficacy of oral pyronaridine for the treatment of acute uncomplicated falciparum malaria in African children. *Clin Infect Dis*. 1998;26:946–953.
149. Rueangweerayut R, et al. Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. *N Engl J Med*. 2012;366:1298–1309.
154. Sagara I, et al. Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial. *Lancet Infect Dis*. 2016;16:189–198.
156. Olliaro P, et al. Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet*. 1996;348:1196–1201.
165. Hasugian AR, et al. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine: superior efficacy and posttreatment prophylaxis against multidrug-resistant *Plasmodium falciparum* and *Plasmodium vivax* malaria. *Clin Infect Dis*. 2007;44:1067–1074.
167. Gasasira AF, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis*. 2008;46:985–991.
175. Lee SJ, et al. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: a pooled analysis of 19, 850 individual patients. *PLoS ONE*. 2017;12:e0168780.
182. Nguyen TH, et al. Post-malaria neurological syndrome. *Lancet*. 1996;348:917–921.
183. Eick-Cost AA, et al. Neuropsychiatric outcomes after mefloquine exposure among U.S. Military Service members. *Am J Trop Med Hyg*. 2017;96:159–166.
198. Martin RE, Kirk K. The malaria parasite's chloroquine resistance transporter is a member of the drug/metabolite transporter superfamily. *Mol Biol Evol*. 2004;21:1938–1949.
199. Laufer MK, et al. Return of chloroquine antimalarial efficacy in Malawi. *N Engl J Med*. 2006;355:1959–1966.
203. Price RN, et al. Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis. *Lancet Infect Dis*. 2014;14:982–991.
208. Grigg MJ, et al. Efficacy of artesunate-mefloquine against high-grade chloroquine-resistant *Plasmodium vivax* malaria in Malaysia: an open-label randomised controlled trial. *Clin Infect Dis*. 2016;62:1403–1411.
221. Price RN, et al. Phenotypic and genotypic characterisation of drug-resistant *Plasmodium vivax*. *Trends Parasitol*. 2012;28:522–529.
238. White NJ, et al. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am J Med*. 1982;73:564–572.
243. White NJ. Optimal regimens of parenteral quinine. *Trans R Soc Trop Med Hyg*. 1995;89:462–464.
252. Krause PJ, et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med*. 2000;343:1454–1458.
264. White NJ, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med*. 1983;309:61–66.
277. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis*. 2004;39:1336–1345.
278. White NJ. Primaquine to prevent transmission of falciparum malaria. *Lancet Infect Dis*. 2013;13:175–181.
283. Bennett JW, et al. Primaquine failure and cytochrome P-450 2D6 in *Plasmodium vivax* malaria. *N Engl J Med*. 2013;369:1381–1382.
286. Douglas NM, et al. Unsupervised primaquine for the treatment of *Plasmodium vivax* malaria relapses in southern Papua: a hospital-based cohort study. *PLoS Med*. 2017;14:e1002379.
290. Centers for Disease Control and Prevention. *CDC Yellow Book 2018: Health Information for International Travel*. New York: Oxford University Press; 2017.
292. Baird JK, et al. Diagnosis and treatment of *Plasmodium vivax* malaria. *Am J Trop Med Hyg*. 2016;95(6 suppl):35–51.
298. Ponsa N, et al. Transmission-blocking activity of tafenoquine (WR-238605) and artelinic acid against naturally circulating strains of *Plasmodium vivax* in Thailand. *Am J Trop Med Hyg*. 2003;69:542–547.
304. Walsh DS, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. *J Infect Dis*. 2004;190:1456–1463.
305. Llanos-Cuentas A, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet*. 2014;383:1049–1058.

306. Shanks GD, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against *Plasmodium falciparum* malaria. *Clin Infect Dis*. 2001;33:1968–1974.
311. Kremsner PG, Looareesuwan S, Chulay JD. Atovaquone and proguanil hydrochloride for treatment of malaria. *J Travel Med*. 1999;6(suppl 1):S18–S20.
312. Shanks GD, et al. Atovaquone and proguanil hydrochloride for prophylaxis of malaria. *J Travel Med*. 1999;6(suppl 1):S21–S27.
316. Lell B, et al. Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet*. 1998;351:709–713.
317. Ling J, et al. Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or *Plasmodium vivax* malaria among migrants to Papua, Indonesia. *Clin Infect Dis*. 2002;35:825–833.
320. Deye GA, et al. Prolonged protection provided by a single dose of atovaquone-proguanil for the chemoprophylaxis of *Plasmodium falciparum* malaria in a human challenge model. *Clin Infect Dis*. 2012;54:232–239.
323. Goodman CD, et al. Parasites resistant to the antimalarial atovaquone fail to transmit by mosquitoes. *Science*. 2016;352:349–353.
347. Ramharter M, et al. Artesunate-clindamycin versus quinine-clindamycin in the treatment of *Plasmodium falciparum* malaria: a randomized controlled trial. *Clin Infect Dis*. 2005;40:1777–1784.

References

1. Jiang JB, et al. Antimalarial activity of mefloquine and qinghaosu. *Lancet*. 1982;2:285–288.
2. Cumming JN, Ploypradith P, Posner GH. Antimalarial activity of artemisinin (qinghaosu) and related trioxanes: mechanism(s) of action. *Adv Pharmacol*. 1997;37:253–297.
3. Marfurt J, et al. Comparative ex vivo activity of novel endoperoxides in multidrug-resistant *Plasmodium falciparum* and *P. vivax*. *Antimicrob Agents Chemother*. 2012;56:5258–5263.
4. Toure OA, et al. A phase 3, double-blind, randomized study of arterolane maleate-piperaquine phosphate vs artemether-lumefantrine for falciparum malaria in adolescent and adult patients in Asia and Africa. *Clin Infect Dis*. 2016;62:964–971.
5. ClinicalTrials.gov ID: NCT02497612, To evaluate the efficacy of a single dose regimen of ferroquine and artefenomel in adults and children with uncomplicated *Plasmodium falciparum* malaria (FALCI). 2015.
6. Phyo AP, et al. Antimalarial activity of artefenomel (OZ439), a novel synthetic antimalarial endoperoxide, in patients with *Plasmodium falciparum* and *Plasmodium vivax* malaria: an open-label phase 2 trial. *Lancet Infect Dis*. 2016;16:61–69.
7. Brockman A, et al. *Plasmodium falciparum* antimalarial drug susceptibility on the north-western border of Thailand during five years of extensive use of artesunate-mefloquine. *Trans R Soc Trop Med Hyg*. 2000;94:537–544.
8. Russell B, et al. Determinants of in vitro drug susceptibility testing of *Plasmodium vivax*. *Antimicrob Agents Chemother*. 2008;52:1040–1045.
9. Keiser J, et al. Effect of artesunate and artemether against *Clonorchis sinensis* and *Opisthorchis viverrini* in rodent models. *Int J Antimicrob Agents*. 2006;28:370–373.
10. Keiser J, et al. Artesunate and artemether are effective fasciolicides in the rat model and in vitro. *J Antimicrob Chemother*. 2006;57:1139–1145.
11. Yang DM, Liew FY. Effects of qinghaosu (artemisinin) and its derivatives on experimental cutaneous leishmaniasis. *Parasitology*. 1993;106(Pt 1):7–11.
12. Pandey AV, et al. Artemisinin, an endoperoxide antimalarial, disrupts the hemoglobin catabolism and heme detoxification systems in malarial parasite. *J Biol Chem*. 1999;274:19383–19388.
13. Robert A, et al. The antimalarial drug artemisinin alkylates heme in infected mice. *Proc Natl Acad Sci USA*. 2005;102:13676–13680.
14. Posner GH, et al. Mechanism-based design, synthesis, and in vitro antimalarial testing of new 4-methylated trioxanes structurally related to artemisinin: the importance of a carbon-centered radical for antimalarial activity. *J Med Chem*. 1994;37:1256–1258.
15. Posner GH, et al. Further evidence supporting the importance of and the restrictions on a carbon-centered radical for high antimalarial activity of 1,2,4-trioxanes like artemisinin. *J Med Chem*. 1995;38:2273–2275.
16. Meshnick SR. Artemisinin: mechanisms of action, resistance and toxicity. *Int J Parasitol*. 2002;32:1655–1660.
17. Batty KT, et al. A pharmacokinetic and pharmacodynamic study of intravenous vs oral artesunate in uncomplicated falciparum malaria. *Br J Clin Pharmacol*. 1998;45:123–129.
18. Ilett KF, et al. The pharmacokinetic properties of intramuscular artesunate and rectal dihydroartemisinin in uncomplicated falciparum malaria. *Br J Clin Pharmacol*. 2002;53:23–30.
19. Newton P, et al. Antimalarial bioavailability and disposition of artesunate in acute falciparum malaria. *Antimicrob Agents Chemother*. 2000;44:972–977.
20. Nealon C, et al. Intramuscular bioavailability and clinical efficacy of artesunate in Gabonese children with severe malaria. *Antimicrob Agents Chemother*. 2002;46:3933–3939.
21. Titulaer HA, et al. The pharmacokinetics of artemisinin after oral, intramuscular and rectal administration to volunteers. *J Pharm Pharmacol*. 1990;42:810–813.
22. Karbwang J, et al. Pharmacokinetics and bioavailability of oral and intramuscular artemether. *Eur J Clin Pharmacol*. 1997;52:307–310.
23. Silamut K, et al. Artemether bioavailability after oral or intramuscular administration in uncomplicated falciparum malaria. *Antimicrob Agents Chemother*. 2003;47:3795–3798.
24. Hien TT, et al. Comparative pharmacokinetics of intramuscular artesunate and artemether in patients with severe falciparum malaria. *Antimicrob Agents Chemother*. 2004;48:4234–4239.
25. Binh TQ, et al. Oral bioavailability of dihydroartemisinin in Vietnamese volunteers and in patients with falciparum malaria. *Br J Clin Pharmacol*. 2001;51:541–546.
26. McGready R, et al. Pharmacokinetics of dihydroartemisinin following oral artesunate treatment of pregnant women with acute uncomplicated falciparum malaria. *Eur J Clin Pharmacol*. 2006;62:367–371.
27. Hassan Alin M, et al. Multiple dose pharmacokinetics of oral artemisinin and comparison of its efficacy with that of oral artesunate in falciparum malaria patients. *Trans R Soc Trop Med Hyg*. 1996;90:61–65.
28. Ilett KF, et al. Glucuronidation of dihydroartemisinin in vivo and by human liver microsomes and expressed UDP-glucuronosyltransferases. *Drug Metab Dispos*. 2002;30:1005–1012.
29. Hendriksen IC, et al. Population pharmacokinetics of intramuscular artesunate in African children with severe malaria: implications for a practical dosing regimen. *Clin Pharmacol Ther*. 2013;93:443–450.
30. Zaloumis SG, et al. Population pharmacokinetics of intravenous artesunate: a pooled analysis of individual data from patients with severe malaria. *CPT Pharmacometrics Syst Pharmacol*. 2014;3:e145.
31. Kloprogge F, et al. Opposite malaria and pregnancy effect on oral bioavailability of artesunate—a population pharmacokinetic evaluation. *Br J Clin Pharmacol*. 2015;80:642–653.
32. Li GQ, et al. Clinical trials of artemisinin and its derivatives in the treatment of malaria in China. *Trans R Soc Trop Med Hyg*. 1994;88(suppl 1):S5–S6.
33. Looareesuwan S, et al. A comparative clinical trial of sequential treatments of severe malaria with artesunate suppository followed by mefloquine in Thailand. *Am J Trop Med Hyg*. 1997;57:348–353.
34. Price R, et al. Artesunate and mefloquine in the treatment of uncomplicated multidrug-resistant hyperparasitaemic falciparum malaria. *Trans R Soc Trop Med Hyg*. 1998;92:207–211.
35. World Health Organization. *Guidelines for the Treatment of Malaria*. Third ed. Geneva: World Health Organization; 2015.
36. Price R, et al. Pharmacokinetics of mefloquine combined with artesunate in children with acute falciparum malaria. *Antimicrob Agents Chemother*. 1999;43:341–346.
37. Simpson JA, et al. Population pharmacokinetics of mefloquine in patients with acute falciparum malaria. *Clin Pharmacol Ther*. 1999;66:472–484.
38. White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B Biol Sci*. 1999;354:739–749.
39. Carrara VI, Zwang J, Ashley EA, et al. Changes in the treatment responses to artesunate-mefloquine on the northwestern border of Thailand during 13 years of continuous deployment. *PLoS ONE*. 2009;4:e4551.
40. Charle P, et al. Artesunate/amodiaquine malaria treatment for Equatorial Guinea (Central Africa). *Am J Trop Med Hyg*. 2013;88:1087–1092.
41. Creek DJ, et al. Pharmacokinetic predictors for recurrent malaria after dihydroartemisinin-piperaquine treatment of uncomplicated malaria in Ugandan infants. *J Infect Dis*. 2013;207:1646–1654.
42. Kakuru A, et al. The effects of ACT treatment and TS prophylaxis on *Plasmodium falciparum* gametocytemia in a cohort of young Ugandan children. *Am J Trop Med Hyg*. 2013;88:736–743.
43. Pasaribu AP, et al. A randomized comparison of dihydroartemisinin-piperaquine and artesunate-amodiaquine combined with primaquine for radical treatment of vivax malaria in Sumatera, Indonesia. *J Infect Dis*. 2013;208:1906–1913.
44. Price RN, et al. Effects of artemisinin derivatives on malaria transmissibility. *Lancet*. 1996;347:1654–1658.
45. Sawa P, et al. Malaria transmission after artemether-lumefantrine and dihydroartemisinin-piperaquine: a randomized trial. *J Infect Dis*. 2013;207:1637–1645.
46. Luxemburger C, et al. Oral artesunate in the treatment of uncomplicated hyperparasitemic falciparum malaria. *Am J Trop Med Hyg*. 1995;53:522–525.
47. Dondorp A, et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. 2005;366:717–725.
48. Dondorp AM, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*. 2010;376:1647–1657.
49. Karunajeewa HA, et al. Rectal administration of artemisinin derivatives for the treatment of malaria. *JAMA*. 2007;297:2381–2390.
50. Gomes MF, et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet*. 2009;373:557–566.
51. Denis MB, et al. Efficacy of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Cambodia. *Trop Med Int Health*. 2006;11:1800–1807.
52. Amaratunga C, et al. Artemisinin-resistant *Plasmodium falciparum* in Pursat province, western Cambodia: a parasite clearance rate study. *Lancet Infect Dis*. 2012;12:851–858.
53. Bethell D, et al. Artesunate dose escalation for the treatment of uncomplicated malaria in a region of reported artemisinin resistance: a randomized clinical trial. *PLoS ONE*. 2011;6:e19283.
54. Ashley EA, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*. 2014;371:411–423.
55. Saralamba S, et al. Intrahost modeling of artemisinin resistance in *Plasmodium falciparum*. *Proc Natl Acad Sci USA*. 2011;108:397–402.
56. Ariey F, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. *Nature*. 2014;505:50–55.
57. Tun KM, et al. Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker. *Lancet Infect Dis*. 2015;15:415–421.
58. Takala-Harrison S, et al. Independent emergence of artemisinin resistance mutations among *Plasmodium falciparum* in Southeast Asia. *J Infect Dis*. 2015;211:670–679.
59. Price R, et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg*. 1999;60:547–555.
60. Taylor WR, White NJ. Antimalarial drug toxicity: a review. *Drug Saf*. 2004;27:25–61.
61. Leonardi E, et al. Severe allergic reactions to oral artesunate: a report of two cases. *Trans R Soc Trop Med Hyg*. 2001;95:182–183.
62. Brewer TG, et al. Fatal neurotoxicity of arteether and artemether. *Am J Trop Med Hyg*. 1994;51:251–259.
63. Brewer TG, et al. Neurotoxicity in animals due to arteether and artemether. *Trans R Soc Trop Med Hyg*. 1994;88(suppl 1):S33–S36.
64. Nontprasert A, et al. Neuropathologic toxicity of artemisinin derivatives in a mouse model. *Am J Trop Med Hyg*. 2002;67:423–429.
65. Nontprasert A, et al. Studies of the neurotoxicity of oral artemisinin derivatives in mice. *Am J Trop Med Hyg*. 2000;62:409–412.
66. Elias Z, et al. Neurotoxicity of artemisinin: possible counseling and treatment of side effects. *Clin Infect Dis*. 1999;28:1330–1331.
67. Franco-Paredes C, et al. Neurotoxicity due to antimalarial therapy associated with misdiagnosis of malaria. *Clin Infect Dis*. 2005;40:1710–1711.
68. Miller LG, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria. *N Engl J Med*. 1997;336:1328.
69. Senanayake N, de Silva HJ. Delayed cerebellar ataxia complicating falciparum malaria: a clinical study of 74 patients. *J Neurol*. 1994;241:456–459.
70. Newton PN, Day NP, White NJ. Misattribution of central nervous system dysfunction to artesunate. *Clin Infect Dis*. 2005;41:1687–1688, author reply 1688.
71. Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial agents. Fact or fiction? *Drug Saf*. 1995;12:370–383.
72. Kissinger E, et al. Clinical and neurophysiological study of the effects of multiple doses of artemisinin on brain-stem function in Vietnamese patients. *Am J Trop Med Hyg*. 2000;63:48–55.
73. Van Vugt M, et al. A case-control auditory evaluation of patients treated with artemisinin derivatives for multidrug-resistant *Plasmodium falciparum* malaria. *Am J Trop Med Hyg*. 2000;62:65–69.
74. Chan XHS, et al. Risk of sudden unexplained death after use of dihydroartemisinin-piperaquine for malaria: a systematic review and Bayesian meta-analysis. *Lancet Infect Dis*. 2018;18:913–923.
75. Rolling T, et al. Delayed hemolysis after treatment with parenteral artesunate in African children with severe malaria—a double-center prospective study. *J Infect Dis*. 2014;209:1921–1928.
76. Zoller T, et al. Intravenous artesunate for severe malaria in travelers, Europe. *Emerg Infect Dis*. 2011;17:771–777.
77. Jaureguiberry S, et al. Postartesunate delayed hemolysis is a predictable event related to the lifesaving effect of artemisinins. *Blood*. 2014;124:167–175.
78. Longo M, et al. Effects of the antimalarial drug dihydroartemisinin (DHA) on rat embryos in vitro. *Reprod Toxicol*. 2006;21:83–93.
79. Deen JL, et al. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. 2001;95:424–428.
80. McGready R, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. *Clin Infect Dis*. 2001;33:2009–2016.

81. McGready R, Nosten F. The Thai-Burmese border: drug studies of *Plasmodium falciparum* in pregnancy. *Ann Trop Med Parasitol*. 1999;93(suppl 1):S19–S23.
82. Nosten F, et al. The effects of mefloquine treatment in pregnancy. *Clin Infect Dis*. 1999;28:808–815.
83. McGready R, et al. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg*. 1998;92:430–433.
84. Manyando C, et al. A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated *Plasmodium falciparum* malaria during pregnancy. *Malar J*. 2012;11:141.
85. Moore KA, et al. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. *Lancet Infect Dis*. 2016;16:576–583.
86. Ezzet F, et al. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother*. 2000;44:697–704.
87. White NJ, van Vugt M, Ezzet F. Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet*. 1999;37:105–125.
88. Ashley EA, et al. How much fat is necessary to optimize lumefantrine oral bioavailability? *Trop Med Int Health*. 2007;12:195–200.
89. McGready R, et al. The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. *Eur J Clin Pharmacol*. 2006;62:1021–1031.
90. Ezzet F, Mull R, Karbwang J. Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients. *Br J Clin Pharmacol*. 1998;46:553–561.
91. Price RN, et al. Molecular and pharmacological determinants of the therapeutic response to artemether-lumefantrine in multidrug-resistant *Plasmodium falciparum* malaria. *Clin Infect Dis*. 2006;42:1570–1577.
92. Falade C, et al. Efficacy and safety of artemether-lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg*. 2005;99:459–467.
93. Makanga M, et al. Efficacy and safety of the six-dose regimen of artemether-lumefantrine in pediatrics with uncomplicated *Plasmodium falciparum* malaria: a pooled analysis of individual patient data. *Am J Trop Med Hyg*. 2006;74:991–998.
94. Abdulla S, et al. Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. *Lancet*. 2008;372:1819–1827.
95. Worldwide Antimalarial Resistance Network (WWARN) AL Dose Impact Study Group. The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data. *Lancet Infect Dis*. 2015;15:692–702.
96. Lefevre G, et al. Pharmacokinetic interaction trial between co-artemether and mefloquine. *Eur J Pharm Sci*. 2000;10:141–151.
97. Lefevre G, et al. Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet) with concomitant administration of ketoconazole in healthy subjects. *Br J Clin Pharmacol*. 2002;54:485–492.
98. Price RN, et al. Mefloquine resistance in *Plasmodium falciparum* and increased *pfmdr1* gene copy number. *Lancet*. 2004;364:438–447.
99. Humphreys GS, et al. Amodiaquine and artemether-lumefantrine select distinct alleles of the *Plasmodium falciparum mdr1* gene in Tanzanian children treated for uncomplicated malaria. *Antimicrob Agents Chemother*. 2007;51:991–997.
100. Sisowath C, et al. In vivo selection of *Plasmodium falciparum* pfmdr1 86N coding alleles by artemether-lumefantrine (Coartem). *J Infect Dis*. 2005;191:1014–1017.
101. Venkatesan M, et al. Polymorphisms in *Plasmodium falciparum* chloroquine resistance transporter and multidrug resistance 1 genes: parasite risk factors that affect treatment outcomes for *P. falciparum* malaria after artemether-lumefantrine and artesunate-amodiaquine. *Am J Trop Med Hyg*. 2014;91:833–843.
102. Bakshi R, et al. An integrated assessment of the clinical safety of artemether-lumefantrine: a new oral fixed-dose combination antimalarial drug. *Trans R Soc Trop Med Hyg*. 2000;94:419–424.
103. Lefevre G, et al. Interaction trial between artemether-lumefantrine (Riamet) and quinine in healthy subjects. *J Clin Pharmacol*. 2002;42:1147–1158.
104. Piola P, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. *Lancet Infect Dis*. 2010;10:762–769.
105. Rulisa S, et al. Pharmacovigilance of artemether-lumefantrine in pregnant women followed until delivery in Rwanda. *Malar J*. 2012;11:225.
106. McGready R, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated *Plasmodium falciparum* treatment in pregnancy. *PLoS Med*. 2008;5:e253.
107. PREGACT Study Group, et al. Four artemisinin-based treatments in African pregnant women with malaria. *N Engl J Med*. 2016;374:913–927.
108. Tarning J, et al. Population pharmacokinetics of lumefantrine in pregnant women treated with artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria. *Antimicrob Agents Chemother*. 2009;53:3837–3846.
109. Mosha D, et al. Population pharmacokinetics and clinical response for artemether-lumefantrine in pregnant and nonpregnant women with uncomplicated *Plasmodium falciparum* malaria in Tanzania. *Antimicrob Agents Chemother*. 2014;58:4583–4592.
110. Davis TM, et al. Piperaquine: a resurgent antimalarial drug. *Drugs*. 2005;65:75–87.
111. Nosten F, White NJ. Artemisinin-based combination treatment of falciparum malaria. *Am J Trop Med Hyg*. 2007;77(6 suppl):181–192.
112. Hung TY, et al. Population pharmacokinetics of piperaquine in adults and children with uncomplicated falciparum or vivax malaria. *Br J Clin Pharmacol*. 2004;57:253–262.
113. Karunajeewa HA, et al. Pharmacokinetics and efficacy of piperaquine and chloroquine in Melanesian children with uncomplicated malaria. *Antimicrob Agents Chemother*. 2008;52:237–243.
114. Roshammar D, et al. Pharmacokinetics of piperaquine after repeated oral administration of the antimalarial combination CV8 in 12 healthy male subjects. *Eur J Clin Pharmacol*. 2006.
115. Myint HY, et al. Efficacy and safety of dihydroartemisinin-piperaquine. *Trans R Soc Trop Med Hyg*. 2007;101:858–866.
116. Hoglund RM, et al. Population pharmacokinetic properties of piperaquine in falciparum malaria: an individual participant data meta-analysis. *PLoS Med*. 2017;14:e1002212.
117. WorldWide Antimalarial Resistance Network (WWARN) DP Study Group. The effect of dosing regimens on the antimalarial efficacy of dihydroartemisinin-piperaquine: a pooled analysis of individual patient data. *PLoS Med*. 2013;10:e1001564, discussion e1001564.
118. Nguyen TC, et al. Pharmacokinetics of the antimalarial drug piperaquine in healthy Vietnamese subjects. *Am J Trop Med Hyg*. 2008;79:620–623.
119. Sim IK, Davis TM, Ilett KF. Effects of a high-fat meal on the relative oral bioavailability of piperaquine. *Antimicrob Agents Chemother*. 2005;49:2407–2411.
120. Hai TN, et al. The influence of food on the pharmacokinetics of piperaquine in healthy Vietnamese volunteers. *Acta Trop*. 2008;107:145–149.
121. Price RN, Dorsey G, Nosten F. Antimalarial therapies in children from Papua New Guinea. *N Engl J Med*. 2009;360:1254.
122. Karunajeewa HA, et al. A trial of combination antimalarial therapies in children from Papua New Guinea. *N Engl J Med*. 2008;359:2545–2557.
123. Kamya MR, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of malaria: a randomized trial. *PLoS Clin Trials*. 2007;2:e20.
124. Nambozi M, et al. Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Zambian children. *Malar J*. 2011;10:50.
125. Yeka A, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda. *PLoS ONE*. 2008;3:e2390.
126. Ratcliff A, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. *Lancet*. 2007;369:757–765.
127. Valecha N, et al. An open-label, randomised study of dihydroartemisinin-piperaquine versus artesunate-mefloquine for falciparum malaria in Asia. *PLoS ONE*. 2010;5:e11880.
128. Duru V, et al. *Plasmodium falciparum* dihydroartemisinin-piperaquine failures in Cambodia are associated with mutant K13 parasites presenting high survival rates in novel piperaquine in vitro assays: retrospective and prospective investigations. *BMC Med*. 2015;13:305.
129. Leang R, et al. Efficacy of dihydroartemisinin-piperaquine for treatment of uncomplicated *Plasmodium falciparum* and *Plasmodium vivax* in Cambodia, 2008 to 2010. *Antimicrob Agents Chemother*. 2013;57:818–826.
130. Amato R, et al. Genetic markers associated with dihydroartemisinin-piperaquine failure in *Plasmodium falciparum* malaria in Cambodia: a genotype-phenotype association study. *Lancet Infect Dis*. 2017;17:164–173.
131. Witkowski B, et al. A surrogate marker of piperaquine-resistant *Plasmodium falciparum* malaria: a phenotype-genotype association study. *Lancet Infect Dis*. 2017;17:174–183.
132. Zani B, et al. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database Syst Rev*. 2014;(1):Cd010927.
133. Karunajeewa HA, et al. Disposition of artesunate and dihydroartemisinin after administration of artesunate suppositories in children from Papua New Guinea with uncomplicated malaria. *Antimicrob Agents Chemother*. 2004;48:2966–2972.
134. Mytton OT, et al. Electrocardiographic safety evaluation of dihydroartemisinin piperaquine in the treatment of uncomplicated falciparum malaria. *Am J Trop Med Hyg*. 2007;77:447–450.
135. Chang C, Lin-Hua T, Jantanavivat C. Studies on a new antimalarial compound: pyronaridine. *Trans R Soc Trop Med Hyg*. 1992;86:7–10.
136. Olliaro PL, Trigg PI. Status of antimalarial drugs under development. *Bull World Health Organ*. 1995;73:565–571.
137. Druilhe P, et al. Improved assessment of *Plasmodium vivax* response to antimalarial drugs by a colorimetric double-site Plasmodium lactate dehydrogenase antigen capture enzyme-linked immunosorbent assay. *Antimicrob Agents Chemother*. 2007;51:2112–2116.
138. Ringwald P, et al. In vitro activities of pyronaridine, alone and in combination with other antimalarial drugs, against *Plasmodium falciparum*. *Antimicrob Agents Chemother*. 1999;43:1525–1527.
139. Vivas L, et al. Anti-malarial efficacy of pyronaridine and artesunate in combination in vitro and in vivo. *Acta Trop*. 2008;105:222–228.
140. Price RN, et al. In vitro activity of pyronaridine against multidrug-resistant *Plasmodium falciparum* and *Plasmodium vivax*. *Antimicrob Agents Chemother*. 2010;54:5146–5150.
141. Brice BK, et al. In vitro susceptibility of *Plasmodium falciparum* isolates from Abidjan, Cote d'Ivoire, to artemisinin, chloroquine, dihydroartemisinin and pyronaridine. *Tanzan J Health Res*. 2010;12:73–79.
142. Kurth F, et al. In vitro activity of pyronaridine against *Plasmodium falciparum* and comparative evaluation of anti-malarial drug susceptibility assays. *Malar J*. 2009;8:79.
143. Pradines B, et al. In vitro activities of benflumetol against 158 Senegalese isolates of *Plasmodium falciparum* in comparison with those of standard antimalarial drugs. *Antimicrob Agents Chemother*. 1999;43:418–420.
144. Croft SL, et al. Review of pyronaridine anti-malarial properties and product characteristics. *Malar J*. 2012;11:270.
145. Sagara I, Beavogui AH, Zongo I, et al. Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial. *Lancet Infect Dis*. 2016;16:189–198.
146. Ringwald P, Bickii J, Basco L. Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet*. 1996;347:24–28.
147. Ringwald P, Bickii J, Basco LK. Efficacy of oral pyronaridine for the treatment of acute uncomplicated falciparum malaria in African children. *Clin Infect Dis*. 1998;26:946–953.
148. Ramharter M, et al. Fixed-dose pyronaridine-artesunate combination for treatment of uncomplicated falciparum malaria in pediatric patients in Gabon. *J Infect Dis*. 2008;198:911–919.
149. Rueangweerayut R, et al. Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. *N Engl J Med*. 2012;366:1298–1309.
150. Tshefu AK, et al. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial. *Lancet*. 2010;375:1457–1467.
151. Poravuth Y, et al. Pyronaridine-artesunate versus chloroquine in patients with acute *Plasmodium vivax* malaria: a randomized, double-blind, non-inferiority trial. *PLoS ONE*. 2011;6:e14501.
152. Ramanathan S, et al. A new and simple solid-phase extraction method for LC determination of pyronaridine in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2005;824:45–50.
153. Kayentao K, et al. Pyronaridine-artesunate granules versus artemether-lumefantrine crushed tablets in

children with *Plasmodium falciparum* malaria: a randomized controlled trial. *Malar J*. 2012;11:364.

154. Sagara I, et al. Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial. *Lancet Infect Dis*. 2016;16:189–198.
155. Hatton CS, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet*. 1986;1:411–414.
156. Olliaro P, et al. Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet*. 1996;348:1196–1201.
157. Molta NB, et al. Amodiaquine treatment of uncomplicated malaria in children, in an area of chloroquine-resistant *Plasmodium falciparum* in north-central Nigeria. *Ann Trop Med Parasitol*. 2003;97:663–669.
158. Sendagire H, et al. Rapid increase in resistance of *Plasmodium falciparum* to chloroquine-Fansidar in Uganda and the potential of amodiaquine-Fansidar as a better alternative. *Acta Trop*. 2005;95:172–182.
159. Sowunmi A, et al. Randomized comparison of chloroquine and amodiaquine in the treatment of acute, uncomplicated, *Plasmodium falciparum* malaria in children. *Ann Trop Med Parasitol*. 2001;95:549–558.
160. Sa JM, et al. Geographic patterns of *Plasmodium falciparum* drug resistance distinguished by differential responses to amodiaquine and chloroquine. *Proc Natl Acad Sci USA*. 2009;106:18883–18889.
161. Sa JM, Twu O. Protecting the malaria drug arsenal: halting the rise and spread of amodiaquine resistance by monitoring the PfCRT SVMNT type. *Malar J*. 2010;9:374.
162. Pussard E, et al. Disposition of monodesethylamodiaquine after a single oral dose of amodiaquine and three regimens for prophylaxis against *Plasmodium falciparum* malaria. *Eur J Clin Pharmacol*. 1987;33:409–414.
163. Sondo P, et al. Effectiveness and safety of artemether-lumefantrine versus artesunate-amodiaquine for unsupervised treatment of uncomplicated falciparum malaria in patients of all age groups in Nanoro, Burkina Faso: a randomized open label trial. *Malar J*. 2015;14:325.
164. Yeka A, et al. Artesunate/amodiaquine versus artemether/lumefantrine for the treatment of uncomplicated malaria in Uganda: a randomized trial. *J Infect Dis*. 2016;213:1134–1142.
165. Hasugian AR, et al. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine: superior efficacy and posttreatment prophylaxis against multidrug-resistant *Plasmodium falciparum* and *Plasmodium vivax* malaria. *Clin Infect Dis*. 2007;44:1067–1074.
166. Hasugian AR, et al. In vivo and in vitro efficacy of amodiaquine monotherapy for treatment of infection by chloroquine-resistant *Plasmodium vivax*. *Antimicrob Agents Chemother*. 2009;53:1094–1099.
167. Gasasira AF, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis*. 2008;46:985–991.
168. Zhang J, Krugliak M, Ginsburg H. The fate of ferriprotorphyrin IX in malaria infected erythrocytes in conjunction with the mode of action of antimalarial drugs. *Mol Biochem Parasitol*. 1999;99:129–141.
169. Crevoisier C, et al. Food increases the bioavailability of mefloquine. *Eur J Clin Pharmacol*. 1997;53:135–139.
170. Palmer KJ, Holliday SM, Brogden RN. Mefloquine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*. 1993;45:430–475.
171. Looareesuwan S, et al. Studies of mefloquine bioavailability and kinetics using a stable isotope technique: a comparison of Thai patients with falciparum malaria and healthy Caucasian volunteers. *Br J Clin Pharmacol*. 1987;24:37–42.
172. Pennie RA, Koren G, Crevoisier C. Steady state pharmacokinetics of mefloquine in long-term travellers. *Trans R Soc Trop Med Hyg*. 1993;87:459–462.
173. Hellgren U, et al. Enantioselective pharmacokinetics of mefloquine during long-term intake of the prophylactic dose. *Br J Clin Pharmacol*. 1997;44:119–124.
173a. Phyo AP, Ashley EA, Anderson TJC, et al. Declining efficacy of artemisinin combination therapy against *P. Falciparum* malaria on the Thai–Myanmar border (2003–2013): the role of parasite genetic factors. *Clin Infect Dis*. 2016;63:784–791.
174. Ashley EA, et al. Population pharmacokinetic assessment of a new regimen of mefloquine used in combination treatment of uncomplicated falciparum malaria. *Antimicrob Agents Chemother*. 2006;50:2281–2285.
175. Lee SJ, et al. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: a pooled analysis of 19, 850 individual patients. *PLoS ONE*. 2017;12:e0168780.
176. Bryson HM, Goa KL. Halofantrine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic potential. *Drugs*. 1992;43:236–258.
177. Wilson CM, et al. Amplification of pfmdr 1 associated with mefloquine and halofantrine resistance in *Plasmodium falciparum* from Thailand. *Mol Biochem Parasitol*. 1993;57:151–160.
178. World Health Organization. Mefloquine: update on safety issues. *WHO Drug Info*. 1996;10:58–61.
179. ter Kuile FO, et al. Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bull World Health Organ*. 1995;73:631–642.
180. Steffen R, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. *Lancet*. 1993;341:1299–1303.
181. Weinke T, et al. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg*. 1991;45:86–91.
182. Nguyen TH, et al. Post-malaria neurological syndrome. *Lancet*. 1996;348:917–921.
183. Eick-Cost AA, et al. Neuropsychiatric outcomes after mefloquine exposure among U.S. Military Service members. *Am J Trop Med Hyg*. 2017;96:159–166.
184. Sowunmi A, et al. Neuropsychiatric side effects of mefloquine in Africans. *Trans R Soc Trop Med Hyg*. 1993;87:462–463.
185. Jallon P. Use of mefloquine in epileptic patients. *J Neurol Neurosurg Psychiatry*. 1988;51:732.
186. Nosten F, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1:1–15.
187. Loeb RF. Activity of a new antimalarial agent, pentaquine (SN 13,276). *J Am Med Assoc*. 1946;132:321–323.
188. Aylward JM. Hydroxychloroquine and chloroquine: assessing the risk of retinal toxicity. *J Am Optom Assoc*. 1993;64:787–797.
189. Egan TJ. Chloroquine and primaquine: combining old drugs as a new weapon against falciparum malaria? *Trends Parasitol*. 2006;22:235–237.
190. Minker E, Ivan J. Experimental and clinicopharmacological study of rectal absorption of chloroquine. *Acta Physiol Hung*. 1991;77:237–248.
191. Westman L, et al. Rectal administration of chloroquine for treatment of children with malaria. *Trans R Soc Trop Med Hyg*. 1994;88:446.
192. Gustafsson LL, et al. Chloroquine excretion following malaria prophylaxis. *Br J Clin Pharmacol*. 1987;24:221–224.
193. Salako LA, Walker O, Iyun AO. Pharmacokinetics of chloroquine in renal insufficiency. *Afr J Med Med Sci*. 1984;13:177–182.
194. Price RN, Douglas NM, Anstey NM. New developments in *Plasmodium vivax* malaria: severe disease and the rise of chloroquine resistance. *Curr Opin Infect Dis*. 2009;22:430–435.
195. Alving AS, et al. Potentiation of the curative action of primaquine in vivax malaria by quinine and chloroquine. *J Lab Clin Med*. 1955;46:301–306.
196. Martin SK, Oduola AM, Milhous WK. Reversal of chloroquine resistance in *Plasmodium falciparum* by verapamil. *Science*. 1987;235:899–901.
197. Su X, et al. Complex polymorphisms in an approximately 330 kDa protein are linked to chloroquine-resistant *P. falciparum* in Southeast Asia and Africa. *Cell*. 1997;91:593–603.
198. Martin RE, Kirk K. The malaria parasite's chloroquine resistance transporter is a member of the drug/metabolite transporter superfamily. *Mol Biol Evol*. 2004;21:1938–1949.
199. Laufer MK, et al. Return of chloroquine antimalarial efficacy in Malawi. *N Engl J Med*. 2006;355:1959–1966.
200. Kebede S, et al. Return of chloroquine-sensitive *Plasmodium falciparum* parasites and emergence of chloroquine-resistant *Plasmodium vivax* in Ethiopia. *Malar J*. 2014;13.
201. Kiarie WC, et al. Chloroquine sensitivity: diminished prevalence of chloroquine-resistant gene marker *pfcrt-76* 13 years after cessation of chloroquine use in Msambweni, Kenya. *Malar J*. 2015;14:328.
202. Mohammed A, et al. Trends in chloroquine resistance marker, *Pfcrt-K76T* mutation ten years after chloroquine withdrawal in Tanzania. *Malar J*. 2013;12:415.
203. Price RN, et al. Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis. *Lancet Infect Dis*. 2014;14:982–991.
204. Worldwide Antimalarial Resistance Network. Extracted Data From *P. vivax* Antimalarial Efficacy Study Sites; 2013. http://www.wwarn.org/tools-resources/extracted-data-p-vivax-antimalarial-efficacy-study-sites.
205. Fryauff DJ, et al. Chloroquine-resistant *Plasmodium vivax* in transmigration settlements of West Kalimantan, Indonesia. *Am J Trop Med Hyg*. 1998;59:513–518.
206. Sutanto I, et al. Evaluation of chloroquine therapy for vivax and falciparum malaria in southern Sumatra, western Indonesia. *Malar J*. 2010;9:52.
207. Sutanto I, et al. Resistance to chloroquine by *Plasmodium vivax* at Alor in the Lesser Sundas Archipelago in eastern Indonesia. *Am J Trop Med Hyg*. 2009;81:338–342.
208. Grigg MJ, et al. Efficacy of artesunate-mefloquine against high-grade chloroquine-resistant *Plasmodium vivax* malaria in Malaysia: an open-label randomised controlled trial. *Clin Infect Dis*. 2016;62:1403–1411.
209. Phan GT, et al. Artemisinin or chloroquine for blood stage *Plasmodium vivax* malaria in Vietnam. *Trop Med Int Health*. 2002;7:858–864.
210. Guthmann JP, et al. *Plasmodium vivax* resistance to chloroquine in Dawei, southern Myanmar. *Trop Med Int Health*. 2008;13:91–98.
211. Singh RK. Emergence of chloroquine-resistant vivax malaria in south Bihar (India). *Trans R Soc Trop Med Hyg*. 2000;94:327.
212. de Santana Filho FS, et al. Chloroquine-resistant *Plasmodium vivax,* Brazilian Amazon. *Emerg Infect Dis*. 2007;13:1125.
213. Marques MM, et al. *Plasmodium vivax* chloroquine resistance and anemia in the western Brazilian Amazon. *Antimicrob Agents Chemother*. 2014;58:342–347.
214. Ruebush TK, et al. Chloroquine-resistant *Plasmodium vivax* malaria in Peru. *Am J Trop Med Hyg*. 2003;69:548–552.
215. Soto J, et al. *Plasmodium vivax* clinically resistant to chloroquine in Colombia. *Am J Trop Med Hyg*. 2001;65:90–93.
216. Phillips EJ, Keystone JS, Kain KC. Failure of combined chloroquine and high-dose primaquine therapy for *Plasmodium vivax* malaria acquired in Guyana, South America. *Clin Infect Dis*. 1996;23:1171–1173.
217. Kurcer MA, Simsek Z, Kurcer Z. The decreasing efficacy of chloroquine in the treatment of *Plasmodium vivax* malaria, in Sanliurfa, south-eastern Turkey. *Ann Trop Med Parasitol*. 2006;100:109–113.
218. Ketema T, Getahun K, Bacha K. Therapeutic efficacy of chloroquine for treatment of *Plasmodium vivax* malaria cases in Halaba district, South Ethiopia. *Parasites & Vectors*. 2011;4:46.
219. Yohannes AM, et al. Confirmed vivax resistance to chloroquine and effectiveness of artemether-lumefantrine for the treatment of vivax malaria in Ethiopia. *Am J Trop Med Hyg*. 2011;84:137–140.
220. Barnadas C, et al. *Plasmodium vivax* resistance to chloroquine in Madagascar: clinical efficacy and polymorphisms in *pvmdr1* and *pvcrt-o* genes. *Antimicrob Agents Chemother*. 2008;4233–4240.
221. Price RN, et al. Phenotypic and genotypic characterisation of drug-resistant *Plasmodium vivax*. *Trends Parasitol*. 2012;28:522–529.
222. Pukrittayakamee S, et al. Therapeutic responses to different antimalarial drugs in vivax malaria. *Antimicrob Agents Chemother*. 2000;1680–1685.
223. Mnyika KS, Kihamia CM. Chloroquine-induced pruritus: its impact on chloroquine utilization in malaria control in Dar es Salaam. *J Trop Med Hyg*. 1991;94:27–31.
224. Looareesuwan S, et al. Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol*. 1986;22:31–36.
225. Essien EE, Afamefuna GC. Chloroquine and its metabolites in human cord blood, neonatal blood, and urine after maternal medication. *Clin Chem*. 1982;28:1148–1152.
226. Easterbrook M. Ocular effects and safety of antimalarial agents. *Am J Med*. 1988;85(4A):23–29.
227. Griffith KS, et al. Treatment of malaria in the United States: a systematic review. *JAMA*. 2007;297:2264–2277.
228. Sanders J. Treatment of malaria with a short course of quinidine. *Am J Trop Med Hyg*. 1935;1:651–660.
229. Peters W, Robinson BL, Ellis DS. The chemotherapy of rodent malaria. XLII. Halofantrine and halofantrine resistance. *Ann Trop Med Parasitol*. 1987;81:639–646.
230. Choi I, Mego JL. Purification of *Plasmodium falciparum* digestive vacuoles and partial characterization of the vacuolar membrane ATPase. *Mol Biochem Parasitol*. 1988;31:71–78.
231. Ginsburg H, Nissani E, Krugliak M. Alkalinization of the food vacuole of malaria parasites by quinoline drugs and alkylamines is not correlated with their antimalarial activity. *Biochem Pharmacol*. 1989;38:2645–2654.
232. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. *Clin Pharmacokinet*. 1996;30:263–299.
233. White NJ, et al. Quinine loading dose in cerebral malaria. *Am J Trop Med Hyg*. 1983;32:1–5.
234. Mansor SM, et al. Effect of *Plasmodium falciparum* malaria infection on the plasma concentration of alpha 1-acid glycoprotein and the binding of quinine in

Malawian children. *Br J Clin Pharmacol*. 1991;32:317–321.

235. Silamut K, et al. Alpha 1-acid glycoprotein (orosomucoid) and plasma protein binding of quinine in falciparum malaria. *Br J Clin Pharmacol*. 1991;32:311–315.
236. Wanwimolruk S, Denton JR. Plasma protein binding of quinine: binding to human serum albumin, alpha 1-acid glycoprotein and plasma from patients with malaria. *J Pharm Pharmacol*. 1992;44:806–811.
237. Winstanley P, et al. Towards optimal regimens of parenteral quinine for young African children with cerebral malaria: the importance of unbound quinine concentration. *Trans R Soc Trop Med Hyg*. 1993;87: 201–206.
238. White NJ, et al. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am J Med*. 1982;73:564–572.
239. Kremsner PG, et al. Quinine plus clindamycin improves chemotherapy of severe malaria in children. *Antimicrob Agents Chemother*. 1995;39:1603–1605.
240. Centers for Disease Prevention and Control. Guidelines for treatment of malaria in the United States; updated July 1, 2013. https://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf. Accessed February 19, 2019.
241. Davis TM, et al. A safe and effective consecutive-infusion regimen for rapid quinine loading in severe falciparum malaria. *J Infect Dis*. 1990;161:1305–1308.
242. Pukrittayakamee S, et al. A study of the factors affecting the metabolic clearance of quinine in malaria. *Eur J Clin Pharmacol*. 1997;52:487–493.
243. White NJ. Optimal regimens of parenteral quinine. *Trans R Soc Trop Med Hyg*. 1995;89:462–464.
244. Wattanagoon Y, et al. Intramuscular loading dose of quinine for falciparum malaria: pharmacokinetics and toxicity. *Br Med J (Clin Res Ed)*. 1986;293:11–13.
245. Tran TH, et al. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. *N Engl J Med*. 1996;335:76–83.
246. van Hensbroek MB, et al. Quinine pharmacokinetics in young children with severe malaria. *Am J Trop Med Hyg*. 1996;54:237–242.
247. Clyde DF. The problem of drug-resistant malaria. *Am J Trop Med Hyg*. 1972;21:736–743.
248. White NJ. Antimalarial drug resistance: the pace quickens. *J Antimicrob Chemother*. 1992;30:571–585.
249. Woodrow CJ, Krishna S. Antimalarial drugs: recent advances in molecular determinants of resistance and their clinical significance. *Cell Mol Life Sci*. 2006;63: 1586–1596.
250. Okombo J, et al. Update on genetic markers of quinine resistance in *Plasmodium falciparum*. *Mol Biochem Parasitol*. 2011;177:77–82.
251. Vannier E, Gewurz BE, Krause PJ. Human babesiosis. *Infect Dis Clin North Am*. 2008;22:469–488, viii–ix.
252. Krause PJ, et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med*. 2000;343: 1454–1458.
253. Sowunmi A, Salako LA. Effect of dose size on the pharmacokinetics of orally administered quinine. *Eur J Clin Pharmacol*. 1996;49:383–386.
254. Claessen FA, et al. Quinine pharmacokinetics: ototoxic and cardiotoxic effects in healthy Caucasian subjects and in patients with falciparum malaria. *Trop Med Int Health*. 1998;3:482–489.
255. Karlsson KK, Berninger E, Alvan G. The effect of quinine on psychoacoustic tuning curves, stapedius reflexes and evoked otoacoustic emissions in healthy volunteers. *Scand Audiol*. 1991;20:83–90.
256. Karlsson KK, et al. Audiometry as a possible indicator of quinine plasma concentration during treatment of malaria. *Trans R Soc Trop Med Hyg*. 1990;84:765–767.
257. Tange RA, et al. Ototoxic reactions of quinine in healthy persons and patients with *Plasmodium falciparum* infection. *Auris Nasus Larynx*. 1997;24:131–136.
258. Bethell DB, et al. Electrocardiographic monitoring in severe falciparum malaria. *Trans R Soc Trop Med Hyg*. 1996;90:266–269.
259. White NJ, Looareesuwan S, Warrell DA. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. *J Cardiovasc Pharmacol*. 1983;5:173–175.
260. Bonington A, et al. Fatal quinine cardiotoxicity in the treatment of falciparum malaria. *Trans R Soc Trop Med Hyg*. 1996;90:305–307.
261. Bateman DN, Dyson EH. Quinine toxicity. *Adverse Drug React Acute Poisoning Rev*. 1986;5:215–233.
262. Guly U, Driscoll P. The management of quinine-induced blindness. *Arch Emerg Med*. 1992;9:317–322.
263. Krishna S, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. *Trans R Soc Trop Med Hyg*. 1994;88:67–73.
264. White NJ, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med*. 1983;309:61–66.
265. Whitty CJ, Edmonds S, Mutabingwa TK. Malaria in pregnancy. *BJOG*. 2005;112:1189–1195.
266. Bruce-Chwatt LJ. Quinine and the mystery of blackwater fever. *Acta Leiden*. 1987;55:181–196.
267. Warrell DA. Pathophysiology of severe falciparum malaria in man. *Parasitology*. 1987;94(suppl):S53–S76.
268. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med*. 2007;357:580–587.
269. Callaway JL, Tate WE. Letter: toxic epidermal necrolysis caused by "gin and tonic". *Arch Dermatol*. 1974;109: 909.
270. Jarratt M, Rudolph A. Letter: toxic epidermal necrolysis. *Arch Dermatol*. 1975;111:132.
271. Colley JC, et al. Toxicity studies with quinine hydrochloride. *Toxicology*. 1989;54:219–226.
272. Tanimura T. Effects on macaque embryos of drugs reported or suspected to be teratogenic to humans. *Acta Endocrinol Suppl (Copenh)*. 1972;166:293–308.
273. West R. Effect of quinine upon auditory nerve. *Am. J. Obst. & Gynec*. 1938;36:8.
274. McGready R, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. *Trans R Soc Trop Med Hyg*. 2002;96:180–184.
275. McGready R, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg*. 2000;94:689–693.
276. Looareesuwan S, et al. Quinine and severe falciparum malaria in late pregnancy. *Acta Leiden*. 1987;55:115–120.
277. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis*. 2004;39:1336–1345.
278. White NJ. Primaquine to prevent transmission of falciparum malaria. *Lancet Infect Dis*. 2013;13:175–181.
279. Constantino L, et al. Metabolism of primaquine by liver homogenate fractions. Evidence for monoamine oxidase and cytochrome P450 involvement in the oxidative deamination of primaquine to carboxyprimaquine. *Exp Toxicol Pathol*. 1999;51:299–303.
280. Ward SA, et al. Pharmacokinetics of primaquine in man. II. Comparison of acute vs chronic dosage in Thai subjects. *Br J Clin Pharmacol*. 1985;19:751–755.
281. Nicholl DD, et al. The disposition of primaquine in the isolated perfused rat liver. Stereoselective formation of the carboxylic acid metabolite. *Biochem Pharmacol*. 1987;36:3365–3369.
282. Schmidt LH, et al. Comparison of the curative antimalarial activities and toxicities of primaquine and its d and l isomers. *Antimicrob Agents Chemother*. 1977;12:51–60.
283. Bennett JW, et al. Primaquine failure and cytochrome P-450 2D6 in *Plasmodium vivax* malaria. *N Engl J Med*. 2013;369:1381–1382.
284. John GK, et al. Primaquine radical cure of *Plasmodium vivax:* a critical review of the literature. *Malar J*. 2012;11:280.
285. Hill DR, et al. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. *Am J Trop Med Hyg*. 2006;75:402–415.
286. Douglas NM, et al. Unsupervised primaquine for the treatment of *Plasmodium vivax* malaria relapses in southern Papua: a hospital-based cohort study. *PLoS Med*. 2017;14:e1002379.
287. Krudsood S, et al. High-dose primaquine regimens against relapse of *Plasmodium vivax* malaria. *Am J Trop Med Hyg*. 2008;78:736–740.
288. Alving AS, et al. Mitigation of the haemolytic effect of primaquine and enhancement of its action against exoerythrocytic forms of the Chesson strain of *Plasmodium vivax* by intermittent regimens of drug administration: a preliminary report. *Bull World Health Organ*. 1960;22:621–631.
289. Smithuis F, et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *Lancet Infect Dis*. 2010;10:673–681.
290. Centers for Disease Control and Prevention. *CDC Yellow Book 2018: Health Information for International Travel*. New York: Oxford University Press; 2017.
291. Beutler E. The hemolytic effect of primaquine and related compounds: a review. *Blood*. 1959;14:103–139.
292. Baird JK, et al. Diagnosis and treatment of *Plasmodium vivax* malaria. *Am J Trop Med Hyg*. 2016;95(6 suppl):35–51.
293. Reeve PA, et al. Acute intravascular haemolysis in Vanuatu following a single dose of primaquine in individuals with glucose-6-phosphate dehydrogenase deficiency. *J Trop Med Hyg*. 1992;95:349–351.
294. Cohen RJ, et al. Methemoglobinemia provoked by malarial chemoprophylaxis in Vietnam. *N Engl J Med*. 1968;279:1127–1131.
295. Clayman CB, et al. Toxicity of primaquine in Caucasians. *J Am Med Assoc*. 1952;149:1563–1568.
296. Vennerstrom JL, et al. 8-Aminoquinolines active against blood stage *Plasmodium falciparum* in vitro inhibit hematin polymerization. *Antimicrob Agents Chemother*. 1999;43:598–602.
297. Coleman RE, Clavin AM, Milhous WK. Gametocytocidal and sporontocidal activity of antimalarials against *Plasmodium berghei* ANKA in ICR mice and *Anopheles stephensi* mosquitoes. *Am J Trop Med Hyg*. 1992;46: 169–182.
298. Ponsa N, et al. Transmission-blocking activity of tafenoquine (WR-238605) and artelinic acid against naturally circulating strains of *Plasmodium vivax* in Thailand. *Am J Trop Med Hyg*. 2003;69:542–547.
299. Brueckner RP, et al. First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial. *Am J Trop Med Hyg*. 1998;58:645–649.
300. Edstein MD, et al. Population pharmacokinetics of the new antimalarial agent tafenoquine in Thai soldiers. *Br J Clin Pharmacol*. 2001;52:663–670.
301. Brueckner RP, et al. Prophylaxis of *Plasmodium falciparum* infection in a human challenge model with WR 238605, a new 8-aminoquinoline antimalarial. *Antimicrob Agents Chemother*. 1998;42:1293–1294.
302. Marcsisin SR, et al. Tafenoquine and NPC-1161B require CYP 2D metabolism for anti-malarial activity: implications for the 8-aminoquinoline class of anti-malarial compounds. *Malar J*. 2014;13:2.
303. Shanks GD, Kain KC, Keystone JS. Malaria chemoprophylaxis in the age of drug resistance. II. Drugs that may be available in the future. *Clin Infect Dis*. 2001;33:381–385.
304. Walsh DS, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. *J Infect Dis*. 2004;190:1456–1463.
305. Llanos-Cuentas A, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet*. 2014;383:1049–1058.

305a. Lacerda MVG, Llanos-Cuentas A, Krudsood S, et al. Single-dose tafenoquine to prevent relapse of *Plasmodium vivax* malaria. *N Engl J Med*. 2019;380:215–228.

305b. Lanos-Cuentos A, Lacerda MVG, Hien TT, et al. Tafenoquine versus primaquine to prevent relapse of *Plasmodium vivax* malaria. *N Engl J Med*. 2019;380:229–241.

306. Shanks GD, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against *Plasmodium falciparum* malaria. *Clin Infect Dis*. 2001;33:1968–1974.
307. Hudson AT, et al. 566C80: a potent broad spectrum anti-infective agent with activity against malaria and opportunistic infections in AIDS patients. *Drugs Exp Clin Res*. 1991;17:427–435.
308. Hughes WT, et al. Efficacy of a hydroxynaphthoquinone, 566C80, in experimental *Pneumocystis carinii* pneumonitis. *Antimicrob Agents Chemother*. 1990;34:225–228.
309. Araujo FG, Huskinson J, Remington JS. Remarkable in vitro and in vivo activities of the hydroxynaphthoquinone 566C80 against tachyzoites and tissue cysts of *Toxoplasma gondii*. *Antimicrob Agents Chemother*. 1991;35:293–299.
310. Canfield CJ, Pudney M, Gutteridge WE. Interactions of atovaquone with other antimalarial drugs against *Plasmodium falciparum* in vitro. *Exp Parasitol*. 1995;80:373–381.
311. Kremsner PG, Looareesuwan S, Chulay JD. Atovaquone and proguanil hydrochloride for treatment of malaria. *J Travel Med*. 1999;6(suppl 1):S18–S20.
312. Shanks GD, et al. Atovaquone and proguanil hydrochloride for prophylaxis of malaria. *J Travel Med*. 1999;6(suppl 1):S21–S27.
313. Fry M, Pudney M. Site of action of the antimalarial hydroxynaphthoquinone, 2-[trans-4-(4'-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone (566C80). *Biochem Pharmacol*. 1992;43:1545–1553.
314. Srivastava IK, Vaidya AB. A mechanism for the synergistic antimalarial action of atovaquone and proguanil. *Antimicrob Agents Chemother*. 1999;43:1334–1339.
315. Haile LG, Flaherty JF. Atovaquone: a review. *Ann Pharmacother*. 1993;27:1488–1494.
316. Lell B, et al. Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet*. 1998;351:709–713.
317. Ling J, et al. Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or *Plasmodium vivax* malaria among migrants to Papua, Indonesia. *Clin Infect Dis*. 2002;35: 825–833.

318. Polhemus ME, et al. Malaria treatment with atovaquone-proguanil in malaria-immune adults: implications for malaria intervention trials and for pre-exposure prophylaxis of malaria. *Antimicrob Agents Chemother*. 2008;52:1493–1495.
319. Shanks GD, Ragama BO, Oloo AJ. Time to reappearance of malaria parasites following various drug treatment regimens in a holoendemic area of western Kenya. *Trans R Soc Trop Med Hyg*. 1999;93:304–305.
320. Deye GA, et al. Prolonged protection provided by a single dose of atovaquone-proguanil for the chemoprophylaxis of *Plasmodium falciparum* malaria in a human challenge model. *Clin Infect Dis*. 2012;54:232–239.
321. Fivelman QL, et al. Malarone treatment failure and in vitro confirmation of resistance of *Plasmodium falciparum* isolate from Lagos, Nigeria. *Malar J*. 2002;1:1.
322. Boggild AK, et al. Failure of atovaquone-proguanil malaria chemoprophylaxis in a traveler to Ghana. *Travel Med Infect Dis*. 2015;13:89–93.
323. Goodman CD, et al. Parasites resistant to the antimalarial atovaquone fail to transmit by mosquitoes. *Science*. 2016;352:349–353.
324. Kazanjian P, et al. *Pneumocystis carinii* cytochrome b mutations are associated with atovaquone exposure in patients with AIDS. *J Infect Dis*. 2001;183:819–822.
325. McFadden DC, et al. Characterization of cytochrome b from *Toxoplasma gondii* and Q(o) domain mutations as a mechanism of atovaquone-resistance. *Mol Biochem Parasitol*. 2000;108:1–12.
326. Wormser GP, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis*. 2010;50:381–386.
327. Falloon J, et al. Atovaquone suspension in HIV-infected volunteers: pharmacokinetics, pharmacodynamics, and TMP-SMX interaction study. *Pharmacotherapy*. 1999;19:1050–1056.
328. Gregson A, Plowe CV. Mechanisms of resistance of malaria parasites to antifolates. *Pharmacol Rev*. 2005;57:117–145.
329. Watkins WM, Sixsmith DG, Chulay JD. The activity of proguanil and its metabolites, cycloguanil and p-chlorophenylbiguanide, against *Plasmodium falciparum* in vitro. *Ann Trop Med Parasitol*. 1984;78:273–278.
330. Fidock DA, Wellems TE. Transformation with human dihydrofolate reductase renders malaria parasites insensitive to WR99210 but does not affect the intrinsic activity of proguanil. *Proc Natl Acad Sci USA*. 1997;94:10931–10936.
331. Pudney M, et al. Atovaquone and proguanil hydrochloride: a review of nonclinical studies. *J Travel Med*. 1999;6(suppl 1):S8–S12.
332. Helsby NA, et al. The multiple dose pharmacokinetics of proguanil. *Br J Clin Pharmacol*. 1993;35:653–656.
333. McLeod R, et al. Levels of pyrimethamine in sera and cerebrospinal and ventricular fluids from infants treated for congenital toxoplasmosis. Toxoplasmosis Study Group. *Antimicrob Agents Chemother*. 1992;36:1040–1048.
334. Clyde DF, Press J, Shute GT. Transfer of pyrimethamine in human milk. *J Trop Med Hyg*. 1956;59:277–284.
335. Craven SA. Letter: photosensitivity to pyrimethamine? *Br. Med. J*. 1974;2:556.
336. Friman G, et al. Agranulocytosis associated with malaria prophylaxis with Maloprim. *Br Med J (Clin Res Ed)*. 1983;286:1244–1245.
337. Israelski DM, Tom C, Remington JS. Zidovudine antagonizes the action of pyrimethamine in experimental infection with *Toxoplasma gondii*. *Antimicrob Agents Chemother*. 1989;33:30–34.
338. Winstanley P, et al. Chlorproguanil/dapsone for uncomplicated *Plasmodium falciparum* malaria in young children: pharmacokinetics and therapeutic range. *Trans R Soc Trop Med Hyg*. 1997;91:322–327.
339. Wiesner J, et al. The plastid-like organelle of apicomplexan parasites as drug target. *Curr Pharm Des*. 2008;14:855–871.
340. Jacobson JM, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. 2001;15:583–589.
341. Nasta P, Chiodera S. Azithromycin for relapsing cerebral toxoplasmosis in AIDS. *AIDS*. 1997;11:1188.
342. Bosch-Driessen LH, et al. A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. *Am J Ophthalmol*. 2002;134:34–40.
343. Andersen SL, et al. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. *Clin Infect Dis*. 1998;26:146–150.
344. Anderson SL, et al. Prophylaxis of *Plasmodium falciparum* malaria with azithromycin administered to volunteers. *Ann Intern Med*. 1995;123:771–773.
345. Heppner DG Jr, et al. Randomized, controlled, double-blind trial of daily oral azithromycin in adults for the prophylaxis of *Plasmodium vivax* malaria in Western Thailand. *Am J Trop Med Hyg*. 2005;73:842–849.
346. Weiss LM. Babesiosis in humans: a treatment review. *Expert Opin Pharmacother*. 2002;3:1109–1115.
347. Ramharter M, et al. Artesunate-clindamycin versus quinine-clindamycin in the treatment of *Plasmodium falciparum* malaria: a randomized controlled trial. *Clin Infect Dis*. 2005;40:1777–1784.

42 Drugs for Protozoal Infections Other Than Malaria

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SHORT VIEW SUMMARY

Definition
- Drugs are included here for leishmaniasis, trypanosomiasis, cryptosporidiosis, trichomoniasis, amebiasis, giardiasis, and toxoplasmosis. Many of these drugs are available only from the Centers for Disease Control and Prevention (CDC, 800-639-3670). See Table 42.1 for recommended dosages.

Leishmaniasis
- Cutaneous and mucosal leishmaniasis can be treated with the antimonials stibogluconate in the United States and meglumine in Latin America, or liposomal amphotericin B. Miltefosine is an alternative. Visceral leishmaniasis (kala-azar) can be treated with liposomal amphotericin B, miltefosine, or an antimonial.

Trypanosomiasis
- Chagas disease can be treated with either nifurtimox or benznidazole, both of which can cause severe side effects. Treatment of human African trypanosomiasis (sleeping sickness) should only be undertaken with input from physicians with relevant experience.

Amebiasis, Giardiasis, and Trichomoniasis
- These diseases are treated with tinidazole or metronidazole.

Cystoisosporiasis
- Trimethoprim plus sulfamethoxazole (TMP-SMX) or pyrimethamine plus sulfadoxine are the drugs of choice. Ciprofloxacin is a less effective alternative.

Cyclosporiasis
- This disease is treated with TMP-SMX.

Cryptosporidiosis
- In immunocompetent patients cryptosporidiosis can be treated with nitazoxanide.

Toxoplasmosis
- Toxoplasmosis acquired during pregnancy should be treated with spiramycin. Early in the infection, spiramycin may decrease the chance of fetal infection.

This chapter includes the antiprotozoal drugs other than those used to treat malaria, namely drugs to treat infections caused by *Leishmania* parasites—African and American trypanosomes, the causes of human African trypanosomiasis (HAT) and Chagas disease, respectively—and drugs used to treat intestinal protozoal infections, particularly giardiasis and amebiasis. The drugs of choice for these infections are summarized in Table 42.1. Doses and alternative drugs are presented in this chapter and in the chapters describing the parasites and the diseases they cause. Drugs for malaria are covered in Chapter 41, sulfonamide drugs are covered in Chapter 34, and metronidazole is covered in Chapter 28.

DRUGS FOR LEISHMANIASIS AND TRYPANOSOMIASIS

The selection of drugs for leishmaniasis is influenced by the geographic location where the infection was acquired and by the clinical features of the infection, particularly its anatomic location. In patients with African trypanosomiasis the region in which the infection was acquired and the presence or absence of spread to the central nervous system (CNS) are critical elements in drug selection. None of the latter factors are relevant in the choice of treatment for Chagas disease. Many of the agents used for treating these diseases can be difficult to obtain, and in the United States several are only available from the Centers for Disease Control and Prevention (CDC). In addition, many of these agents have significant toxicity profiles and complex treatment regimens, so seeking expert advice is advised.

Amphotericin B

The polyene amphotericin B preferentially binds to the membrane sterol ergosterol, which is the primary sterol of *Leishmania* membranes, and less avidly to the principal sterol of mammalian host membranes, which is cholesterol.[1] The mechanism of action of amphotericin B is thought to result from polymerization of molecules and pore formation at membranes where binding occurs, resulting in membrane leakage of various ions.[2] Treatment failure, although uncommon, may be related to changes in sterol metabolism and an ability to resist oxidative stress.[3]

Conventional amphotericin B has demonstrated efficacy for the treatment of cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL).[4] However, toxicity (primarily renal) limits its use, and liposomal amphotericin B has emerged as the preferred therapy because of its lower toxicity. The latter drug was approved by the US Food and Drug Administration (FDA) in 1997 for the treatment of VL. Accumulating case reports and small case series suggest that this agent may also have a role in the treatment of MCL and CL.[5–7] The FDA-approved regimen for liposomal amphotericin B in immunocompetent patients with VL is 21 mg/kg in seven infusions over a 21-day period (3 mg/kg/day on days 1–5, 14, and 21), although success with a single dose of 10 mg/kg has been reported in India.[8,9] The dosing regimens suggested for CL and MCL vary, with some studies reporting success with doses of 3 mg/kg/day given for 6 to 10 days.[5–7] See Chapter 40A for a full discussion of the use and side effects of amphotericin B.

Antimonials

Antimony has been used for medicinal purposes for several centuries, with efficacy for leishmaniasis reported in the early 1900s.[10] Pentavalent antimony Sb(V) is used for treatment of leishmaniasis and is available as stibogluconate (sodium antimony gluconate, Pentostam; Fig. 42.1) and as meglumine antimoniate (Glucantime, France). Generic preparations of the two formulations of Sb(V) are manufactured, one of which has been approved by the World Health Organization (sodium stibogluconate [SSG], Albert David, India). In the United States neither meglumine nor stibogluconate is commercially available, but stibogluconate can be obtained from the CDC Drug Service for civilian physicians and from the US Army Medical Material Development Activity for US military physicians.

The detailed chemical structure of Sb(V) is not fully known, although analysis by electrospray ionization mass spectrometry (ESI-MS) and

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

TABLE 42.1 Drugs for Protozoa Other Than Malaria

INFECTING ORGANISM	TREATMENT OF CHOICE	ALTERNATIVE TREATMENTS
Leishmaniasis: *Leishmania donovani, L. major, L. infantum, L. chagasi, L. mexicana, L. tropica, L. (Viannia)* spp.		
Cutaneous leishmaniasis	Sodium stibogluconate or meglumine antimoniate, 20 mg/kg/day IV or IM × 20 days, or liposomal amphotericin B, 3 mg/kg/day IV × 7–10 doses[a]	Miltefosine, 50 mg PO 2 (30–44 kg) to 3 (≥45 kg) times daily × 28 days
Mucosal leishmaniasis	Liposomal amphotericin B at 20–35 mg/kg (total dose) given as 3 mg/kg IV once daily	Sodium stibogluconate or meglumine antimoniate 20 mg/kg/day IV or IM × 28 days; miltefosine 50 mg PO 2 (30–44 kg) to 3 (≥45 kg) times daily × 28 days; amphotericin B deoxycholate, 1 mg/kg IV qod or daily to a total dose of 20–40 mg/kg
Visceral leishmaniasis	Liposomal amphotericin B, 3 mg/kg/day IV × days 1–5, then at day 14 and 21	Sodium stibogluconate or meglumine antimoniate, 20 mg/kg/day IV or IM × 28 days; miltefosine 50 mg PO 2 (30–44 kg) to 3 (≥45 kg) times daily × 28 days; amphotericin B deoxycholate, 0.5–1 mg/kg/day or qod to a total dose of 15–20 mg/kg[a]
Amebiasis *(Entamoeba histolytica)*	Tinidazole, 2 g PO once daily × 3–5 days	Metronidazole, 500–750 mg PO or IV tid × 7–10 days
Giardiasis (*Giardia lamblia,* also called *G. duodenalis* or *G. intestinalis*)	Tinidazole, 2 g PO once	Metronidazole, 250 mg PO tid × 5–7 days
Trichomoniasis *(Trichomonas vaginalis)*	Tinidazole, 2 g PO once	Metronidazole, 2 g PO once
Cryptosporidiosis (*Cryptosporidium* spp.)	Nitazoxanide, 500 PO bid × 3 days[b]	
American trypanosomiasis (Chagas disease; *Trypanosoma cruzi*)	Benznidazole, 5–7 mg/kg/day PO in two doses × 60 days	Nifurtimox, 8–10 mg/kg/day PO in three to four doses × 90 days
African trypanosomiasis (*Trypanosoma brucei gambiense* [W. African]; *T. b. rhodesiense* [E. African])	Pentamidine/suramin/eflornithine/nifurtimox/melarsoprol	Drug treatment depends on stage of disease (hemolymphatic stage or CNS disease) and on geographic origin (W. or E. African); consult expert guidelines

[a]Not specifically approved by the US Food and Drug Administration for use in this infection.
[b]Relatively ineffective in immunosuppressed patients.
bid, Twice daily; *CNS,* central nervous system; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *qod,* every other day; *tid,* three times daily.

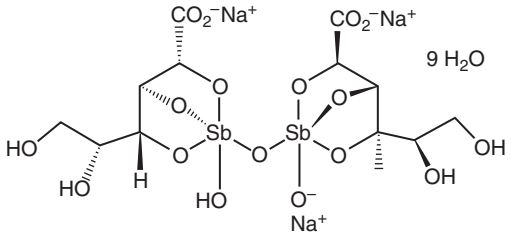

FIG. 42.1 Sodium stibogluconate.

osmolarity measurements suggest that both meglumine antimoniate and stibogluconate contain 1:1, 1:2, 2:2, and 2:3 Sb(V)-ligand complexes. ESI-MS analysis of meglumine antimoniate showed negatively charged 1:1 (mass-to-charge ratio [m/z] 364) and 2:2 (m/z 765) Sb(V)–meglumine antimoniate complexes, supporting the predominance of zwitterionic species in solution. ESI-MS measurements of stibogluconate also demonstrate a mixture of oligomeric structures.[11]

Despite almost a century of use, the mechanism of action of pentavalent antimonials is not well understood. One model suggests that Sb(V) acts as a prodrug and is reduced to the more active/toxic trivalent form of antimony, Sb(III). Sb(III) affects glucose metabolism, fatty-acid beta-oxidation, and adenosine triphosphate (ATP) formation.[12,13] Other specific targets, such as topoisomerase or trypanothione reductase, have been identified.[14,15] Sb(III) also competes with Zn(II) for its binding to the motif CCHC, which is a constituent of zinc-finger domains, suggesting that zinc-finger proteins may be targets of antimony.[16] A second model holds that Sb(V) has intrinsic antileishmanial activity. Sb(V) has been reported to complex with adenine nucleosides, which might act as an inhibitor of *Leishmania* purine transporters or interfere with the purine salvage pathway.[17] A third model suggests that activation of the host immune system is the major mechanism of action for pentavalent antimonials. Sodium antimony gluconate has been shown to induce nitric oxide (NO) synthesis and reactive oxygen species (ROS), with both ROS and NO involved in parasite killing in the early stage of infection and NO in the late stage.[18,19] Sodium antimony gluconate has also been shown to upregulate interferon-γ (IFN-γ) receptors in both *Leishmania donovani*–infected and –uninfected Th1 cells, and in monocytes derived from kala-azar patients treated with sodium antimony gluconate, thus potentially influencing host response by altering IFN-γ responsiveness.[20]

Clinical nonresponse or relapse after treatment with Sb(V) has become problematic in certain geographic areas, most notably the Bihar State, India, and the Terai regions of Nepal.[21] The mechanism of resistance is not defined, and no biomarker for drug resistance has been identified.[22,23] An intriguing association between arsenic contamination of drinking water and antimonial resistance has been proposed in a mouse model and an underpowered and retrospective analysis.[24,25]

SSG and meglumine antimoniate have similar efficacy and side-effect profiles, and because English-speaking countries primarily use SSG, further discussion will focus on that drug. SSG is provided as a 100-mg antimony/mL solution that contains a preservative, *m*-chlorocresol. The solution should be drawn up through a filter before administration due to the presence of particulates formed by an interaction between the product preservative and the antioxidant in the rubber stopper. SSG is administered parenterally, with the intravenous (IV) route being preferable for patient comfort due to the volume of injection. The recommended dose of SSG is 20 mg/kg per day with no maximum daily dose for a duration of 10 to 30 days, depending on patient and parasite factors.[4] Although painful, SSG can also be directly injected into CL lesions, typically at a dose of 1 to 5 mL of SSG solution injected per session every 3 to 7 days for one to five sessions.[26]

SSG is well absorbed after intramuscular (IM) administration, with a first-order absorption rate constant, rapid distribution, and a slower elimination half-life of about 10 hours.[27,28] The drug is renally excreted, with substantial variability among patients. Administration to patients with renal insufficiency is not recommended, and there are no specific guidelines for dose adjustment with renal or hepatic impairment. SSG should be avoided during pregnancy, with one study reporting abortions during the 16th to 22nd weeks of pregnancy in 11 of 16 treated patients.[29]

Side effects of systemic administration of stibogluconate are common and include asymptomatic elevations in amylase and lipase in most patients. Approximately 50% of patients develop elevations of liver aminotransferase levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and/or electrocardiographic changes (most commonly prolongation of the QT interval and/or T wave changes), both of which resolve with cessation of therapy. Arthralgias and myalgias develop in approximately 50% of patients and can persist for weeks after completion of treatment. Rarer, more serious adverse effects

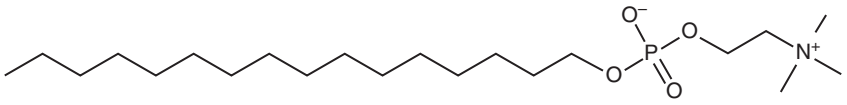

FIG. 42.2 Miltefosine.

include pancreatitis, herpes zoster, and cardiotoxicity.[30–33] To monitor for toxicity, baseline and at least weekly complete blood counts, serum biochemistry, amylase, and electrocardiograms (ECG) are suggested. ECG changes and elevations of amylase, lipase, and hepatic aminotransferase levels are typically transient and may not require cessation of therapy. However, consultation with a provider experienced with the use of SSG is suggested.

Drug interactions with stibogluconate have not been reported, but it is advised that the product be given with caution in patients with cardiovascular disease, a history of ventricular arrhythmias, or other risk factors known to predispose toward QT prolongation, including use of class III antiarrhythmics, such as sotalol and amiodarone. A risk of fatal cardiac arrhythmias has been observed when amphotericin B is administered after stibogluconate during re-treatment of VL.[34]

Triazoles

A variety of triazoles typically used for treatment of fungal infections have been reported to be useful for treating leishmaniasis, most commonly for CL. Fluconazole, itraconazole, and ketoconazole are the drugs most studied in this regard, with varying rates of efficacy.[35] See Chapter 40B for a full discussion of the uses and side effects associated with triazoles.

Miltefosine

Miltefosine (Fig. 42.2) is an oral agent originally developed for treatment of breast cancer and other solid tumors, but its development as an antineoplastic agent was stopped because of dose-limiting gastrointestinal (GI) toxicity. In immunocompetent patients a 28-day regimen has a reported a cure rate of 60% to 80% in MCL and greater than 80% in VL.[36–39] Cure rates for CL have ranged widely by geographic area, perhaps reflecting a species-specific variation in response to therapy.[40] In 2014 the drug was approved by the FDA for the treatment of VL due to *Leishmania donovani*; CL due to *L. braziliensis, L. panamensis*, and *L. guyanensis;* and for MCL due to *L. braziliensis*.

Miltefosine is a member of the alkylphosphocholine class of drugs, which are phosphocholine esters of aliphatic long-chain alcohols. The mechanism of action of miltefosine is incompletely understood but may be related to a disruption of lipid metabolism and other metabolic pathways, with insertion directly into the *Leishmania* cell membrane and/or induction of apoptosis.[41,42] Miltefosine inserts directly within the *Leishmania* plasma membrane, which may be especially relevant when entry into *Leishmania* is inhibited.[43] It inhibits the activity of the AKT protein (also known as protein kinase B [PKB]), which is an important protein within the phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) intracellular signaling pathway, a pathway that is essential for cell survival.[44,45] It also inhibits phophatidylethanol-amine-PC-*N*-methyltransferase, which decreases the production of phosphatidylcholine, the primary phospholipid component of *Leishmania*.[46]

Resistance of *Leishmania* parasites to miltefosine appears to be related to decreased drug accumulation. Resistant lines achieve low drug levels by two independent mechanisms: either by increasing drug efflux, mediated by the overexpression of the ATP-binding cassette (ABC) transporter P-glycoprotein, or by decreasing drug uptake, which is achieved by the inactivation of any one of the two proteins known to be responsible for the miltefosine uptake—the miltefosine transporter LdMT and its beta subunit LdRos3.[47] Resistance may also be related to alterations in fatty-acid and sterol metabolism, which reduce the ability of miltefosine to insert into the plasma membrane.[48]

Miltefosine is administered for 28 days at a dose of 50 mg orally twice daily for persons weighing 30 to 44 kg or 50 mg orally three times daily for those weighing 45 kg or more. Its oral bioavailability has not been determined, but the absolute bioavailability in rats and dogs is 82% and 95%, respectively.[49] The drug has an extremely long triphasic elimination half-life of 30.9 days, with drug detected at least 5 months posttreatment. No data on drug-drug interactions have been reported.[50] Nausea, vomiting, and diarrhea have been consistently reported, and it is recommended that the drug be taken with meals to decrease GI side effects. Elevated creatinine levels are frequently reported, although severe nephrotoxicity is rare. Mild elevations of aminotransferase levels (both ALT and AST) often occur during the first week of treatment.[37,51] In a cohort of soldiers treated with miltefosine, 70% were unable to complete daily military exercises, and 62% reported temporary diminished ejaculate volume.[52] Miltefosine is teratogenic, and thus administration is contraindicated during pregnancy. Because of the drug's long half-life, it is recommended that females of childbearing age use contraception during and for at least 4 months after the standard 28-day treatment regimen.[53] Miltefosine is not recommended for use in women who are breastfeeding.

Paromomycin

Paromomycin (Aminosidine), an aminoglycoside antibiotic, is the only aminoglycoside with activity against *Leishmania*; it also has activity against some other protozoa and cestodes.[54] Although its utility for the treatment of VL has been reported, there are reports of geographic variation in response rates.[55,56] In some studies the combination of paromomycin and stibogluconate has been shown to be effective.[57] Injectable paromomycin is ineffective for the treatment of CL, and mixed results have been reported with topical paromomycin, formulated as an ointment with various additional components for the treatment of CL.[58–60] A randomized study conducted in Tunisia reported that a topical cream containing 15% paromomycin cured 81% of index lesions caused by *Leishmania major*, whereas a study in Panama with CL lesions due to *Leishmania panamensis* reported a 60% cure rate with 15% paromomycin, which was improved to 87% with the addition of 0.5% gentamicin.[61,62] IV paromomycin is not available for use in the United States, but the oral capsule is FDA approved for treatment of intestinal amebiasis. The topical formulation is not approved or commercially available, although compounding recommendations are available.[4]

The mechanism of leishmanicidal activity of paromomycin is poorly understood, with activity proposed to be mediated through inhibition of parasite metabolism and mitochondrial respiration.[63,64] Resistance to paromomycin is readily induced in vitro with contributions from altered membrane fluidity, decreased drug accumulation, increased expression of ABC transporters, and greater tolerance of parasites to host defense mechanisms.[65]

Paromomycin is given at a dose of 11 to 20 mg/kg IM daily for 10 to 21 days for the treatment of VL. As expected, the important aminoglycoside class adverse drug reactions are renal, cochlear, and vestibular toxicity. The rates of adverse reactions reported in clinical trials have been low, although audiometric studies were not performed in most trials. Insufficient data are available regarding the use of paromomycin in pregnant women, although the drug is thought to be safe during lactation, provided the mother and infant have normal renal function.

Oral paromomycin has useful activity for clearance of cyst carriage of *Entamoeba histolytica*, with a small clinical trial indicating that it is more effective than diloxanide for this indication.[66] The dose for this indication and for treatment of *Dientamoeba fragilis* infections is 25 to 35 mg/kg per day in three divided doses for 7 days. The drug shows some activity in human cryptosporidiosis,[54] with most studies reporting on activity in the setting of human immunodeficiency virus (HIV) infection.[67,68] However, available data indicate that the drug is not curative.

Pentamidine

Pentamidine is an aromatic diamidine that is used to treat the hemolymphatic form (stage 1 disease) of both East and West African

trypanosomiasis. It also is a second-line drug for prophylaxis and treatment of *Pneumocystis jirovecii* pneumonia[69,70] and is also used for treatment of leishmaniasis.[71,72] In addition, pentamidine has activity against *Acanthamoeba* spp. and *Balamuthia mandrillaris*.[73,74]

Although the precise mechanism of action of pentamidine has not been determined, it is known that pentamidine affects a wide range of microbial processes, including interaction with trypanosomal kinetoplast DNA; interference with polyamine synthesis by decreasing the activity of ornithine decarboxylase; and inhibition of RNA polymerase, ribosomal function, and the synthesis of nucleic acids and proteins.

IM pentamidine is well absorbed, highly tissue bound, and is excreted slowly over several weeks. Renal clearance is minimal. Its elimination half-life is 12 days,[75] but it can be detected in plasma up to 8 months after a single dose.[76] A steady-state plasma concentration is not attained in persons given daily injections, with extensive accumulation of the drug in visceral tissues, primarily the liver, kidney, adrenal glands, and spleen. Pentamidine does not penetrate the blood-brain barrier well, reaching only 0.5% to 0.8% of plasma concentrations after a course of treatment.[77] Thus it should never be used to treat patients with the CNS form of trypanosomiasis (stage 2 disease).

Resistance to pentamidine has been found in human African trypanosomes that are also resistant to melarsoprol. Recent evidence suggests that the unconventional aquaglyceroporin AQP2 renders cells sensitive to both melarsoprol and pentamidine, and that loss of AQP2 function could explain cases of innate and acquired pentamidine-melarsoprol cross-resistance.[78]

Dosing of pentamidine is not generally modified in patients with renal or liver dysfunction. There are no data regarding the pharmacokinetics of pentamidine in obese patients. In animal models pentamidine is embryocidal but neither teratogenic nor mutagenic.[79] Treatment with pentamidine should be delayed until after the first trimester of pregnancy. The relapse rate in children with trypanosomiasis treated with pentamidine is higher than in adults,[80] and a delayed response in children with leishmaniasis treated with pentamidine has been noted.[81] These observations suggest that the pharmacokinetics of pentamidine in children differ substantially from those in adults, but there are no experimental data to support this concept.

Sterile abscesses can result from IM injections of pentamidine. Hypotension is seen in roughly 15% of patients given the drug, especially if given IV over less than 1 hour. In up to a third of patients pentamidine causes some degree of renal impairment; this is usually mild to moderate and reversible. Electrolyte abnormalities, including hyponatremia, hyperkalemia, hypomagnesemia, and hypocalcemia, are common. Hypoglycemia, resulting from a cytotoxic effect on beta-islet cells and insulin release, is an unpredictable and occasionally lethal complication seen in 15% to 25% of patients, particularly with prolonged therapy, azotemia, or high pentamidine levels.[82,83] Pentamidine can cause severe pancreatitis, resulting in diabetes over the long term. Neutropenia has been noted; anemia and thrombocytopenia are less frequent. Nausea or vomiting is seen in up to one-half of patients, and abnormalities of liver function tests are also common. A variety of electrocardiographic abnormalities, including *torsades de pointes*, have been reported. Data regarding interactions between pentamidine and other drugs are lacking.

Pentamidine is a second-line therapy for leishmaniasis, predominantly used for CL. Efficacy varies widely, with cure rates ranging from 35% with *L. (Viannia) braziliensis* in Peru, to 90% with *L. (Viannia) guyanensis* in Suriname. Use as secondary prophylaxis for VL in a small number of immunocompromised patients has been reported.[84] When used for treatment of CL, the dose is usually 3 to 4 mg/kg every other day for 3 or 4 doses or 2 mg/kg every other day for 7 days. The dose recommended for treatment of mucosal leishmaniasis is 2 to 4 mg/kg every other day or three times per week for 15 or more doses, and for VL it is 4 mg/kg every other day or three times per week for 15 to 30 doses. See Chapter 269 for a further discussion of the use and toxicities of pentamidine for treatment of *P. jirovecii* infection.

Benznidazole

Benznidazole (Fig. 42.3) is a nitroimidazole derivative that is the drug of choice for treating infections with *Trypanosoma cruzi*. The mechanism of action of benznidazole is not known. Benznidazole is readily absorbed, highly lipophilic, and extensively metabolized, with only 5% of the dose excreted unchanged in the urine.[85–87]

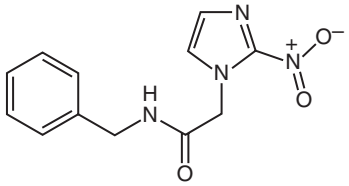

FIG. 42.3 Benznidazole.

Benznidazole is only available in oral form. The dose and duration of treatment are the same regardless of the stage of the infection. No assays are available commercially to determine blood levels, and no data are available to guide dose adjustments in patients with renal or hepatic insufficiency, pregnancy, or in lactating women. It is recommended that benznidazole not be given to such patients. Resistance to benznidazole has been reported[88]; efforts to understand the molecular mechanisms underlying resistance are underway.[89,90] The clinical significance of resistance is unknown, in large measure because compliance is often an issue, and also because assessment of parasitologic cure after treatment is difficult. No assays for testing for resistance to benznidazole are available, and no published data regarding drug-drug interactions are available.

Adverse effects occur in a substantial proportion of patients treated with benznidazole. Peripheral neuropathy and rash are the most commonly reported adverse effects. Granulocytopenia can also occur. On occasion the latter can be severe, and because of this, blood counts should be monitored weekly during the first few weeks of treatment. Adverse effects usually disappear with dose reduction or stopping the drug, although granulocytopenia may take several weeks to resolve. Limited data suggest that there is no relationship between benznidazole levels and the risk of adverse drug reactions.[91] In one sizable study only female gender, increasing age, and duration of treatment were found to be significant risk factors for side effects.[78] It is noteworthy that patients with Chagas disease who undergo cardiac transplantation and who are given benznidazole for management of reactivation of *T. cruzi* have an increased incidence of malignant tumors.[92] However, the incidence of tumors in the general population of patients treated with benznidazole has not been studied.

Benznidazole is widely available in the endemic countries, which include Mexico and all the countries of Central and South America. In the United States benznidazole is available from the CDC Drug Service. Of importance, however, in 2017 the FDA granted accelerated approval to Laboratorio ELEA, a company in Argentina, to market benznidazole for use in children ages 2 to 12 years old with Chagas disease. When benznidazole receives regulatory approval in the United States, obtaining it will become easier.

Fexinidazole

Fexinidazole, a nitroimidazole was discovered in the late 1970s and shown to have useful activity in a murine model of HAT.[93] After a hiatus of 30 years, its development for this indication was resumed by the Drugs for Neglected Diseases initiative (DNDi).[94] Its in vitro inhibitory concentration of 50% against laboratory strains and clinical isolates of *Trypanosoma brucei* ranged between 0.16 and 0.93 μg/mL.[94] Its bioavailability when administered orally ranged from 41% in mice to 10% in dogs. It is well tolerated in single doses from 100 to 3600 mg. It is quickly absorbed and rapidly metabolized in vivo by a wide range of cytochrome P450 (CYP) enzymes, as well as via the human flavin monooxygenase-3 enzyme to at least two biologically active metabolites (a sulfoxide and a sulfone derivative; time of maximum concentration of 2–5 hours and 18–24 hours, respectively). These active metabolites likely account for a significant portion of its antiparasitic effect. Taking the drug with food significantly increases the absorption and plasma concentrations of fexinidazole and its two metabolites by approximately 200%.[95] Its half-life is approximately 11 hours,[95] with most of the drug being excreted by the biliary route. Although fexinidazole shares a class

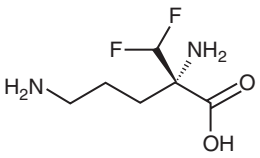

FIG. 42.4 **Eflornithine.**

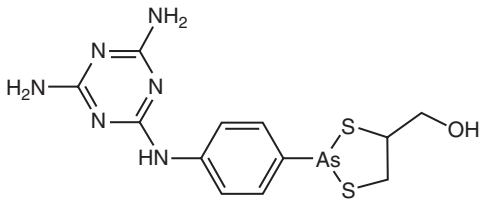

FIG. 42.5 **Melarsoprol.**

effect of nitroimidazoles in being mutagenic in the Ames test, a mutagenic effect has been excluded in mammalian cells and in mice.[94] Distinguishing any side effects of the drug from clinical effects of HAT treatment is difficult. In a phase I study, where the proposed therapeutic dose was administered, the drug was well tolerated, with transient headache and vomiting being reported side effects.[95] In a recently reported phase II/III study,[96] the safety and efficacy of an oral regimen of fexinidazole versus nifurtimox-eflornithine combination therapy (NECT) was evaluated in patients with late-stage HAT caused by *Trypanosoma brucei (T. b.) gambiense*. Patients were randomized 2:1 to once-daily oral fexinidazole in a regimen of 1800 mg/day (days 1–4), then 1200 mg (days 5–10), or to a standard NECT regimen. At 18 months, 239 of 264 (91%) patients given fexinidazole were deemed cured, compared with 124 of 130 (98%) patients given NECT, a difference of −6.4% (97.06% confidence interval [CI], −11.2 to −1.6; $P = .0029$). Treatment-related adverse events, discontinuations, disruptions, or deaths occurred at equivalent rates in the two groups. Based on this study, in November 2018 the European Medicines Agency adopted a positive scientific opinion of this drug as the first all oral agent for treatment of all stages of *T. b. gambiense* HAT.

Eflornithine

Eflornithine (DFMO, Ornidyl; Fig. 42.4) is a fluorinated analogue of ornithine used for treatment of HAT. The drug is effective against all stages of West African HAT, caused by *T. b. gambiense*. However, it lacks activity against East African HAT caused by *T. b. rhodesiense*.

Eflornithine acts as an irreversible suicide inhibitor of ornithine decarboxylase, the first enzyme in the biosynthesis of the polyamines putrescine and spermidine. Interference with polyamine synthesis impairs the ability of the parasite to maintain its redox state and to block reactive oxygen intermediates.[89,97] Polyamines also are essential for parasite cell division. Although the drug has a similar effect on humans, there is a selective effect on trypanosomes because they have a relatively low turnover of ornithine decarboxylase and, as a consequence, a more rapid decrease of polyamines with eflornithine treatment.

Eflornithine can be given IV or orally, but its bioavailability after oral administration is only 54%. Eflornithine readily crosses the blood-brain barrier, and cerebrospinal fluid (CSF) levels are highest in persons with the most severe CNS involvement of the infection.[98] The elimination half-life of eflornithine is 3.3 hours, with greater than 80% excreted in the urine unchanged.[99] Given its predominant renal excretion, dose reduction should occur in patients with renal sufficiency. However, specific data to guide dose adjustments are not available. Dosing need not be adjusted in patients with hepatic dysfunction.

Treatment failures with eflornithine have been reported, with the loss of the gene that encodes the amino-acid transporter TbAAT6 being proposed as the molecular basis of this resistance, at least in *T. b. gambiense*.[100,101] The relative lack of activity of eflornithine against *T. b. rhodesiense* may be attributable to alternate mechanisms.[98,102] At the end of a 14-day course of IV eflornithine, patients who failed therapy had eflornithine CSF trough concentrations of greater than 50 nmol/mL, suggesting parasite resistance to the drug rather than inadequate CSF drug levels as the cause of the failures. The pharmacokinetics of eflornithine in children differ substantially from adults, with mean serum and CSF levels about 60% of levels found in adults; this may explain the higher rate of treatment failure in children.[103]

The most common toxicity of eflornithine is hematologic, with anemia (40%), leukopenia (20% to 30%), and thrombocytopenia (50%) being common. However, these effects are usually mild and without clinical significance. Seizures, associated with higher CSF concentrations, occur more commonly in cases of relapse (12%) than in new cases (4%). An osmotic diarrhea is seen more frequently when eflornithine is given orally. Hearing loss and alopecia have been reported in a few patients. Some patients die during treatment, but this appears to be related to the underlying disease rather than as a result of drug toxicity. In animal models eflornithine is embryotoxic and induces abortions but is not teratogenic[104]; anecdotal data suggest that treatment of pregnant women with eflornithine is associated with abortion.[103]

No data are available concerning interactions between eflornithine and other drugs. However, animal models suggest that eflornithine may be synergistic with other trypanocidal drugs, particularly melarsoprol, because eflornithine reduces the production of trypanothione, a spermidine-glutathione conjugate that is one of the targets of melarsoprol.[105,106]

The use of eflornithine in combination with nifurtimox (NECT) for stage 2 West African HAT is discussed in the subsequent nifurtimox section.

Melarsoprol

Melarsoprol (Fig. 42.5) is an aromatic arsenical that has been used for more than 60 years for treatment of HAT with CNS involvement (stage 2 disease) and for the treatment of hemolymphatic (stage 1 disease) HAT that cannot be effectively treated with suramin or pentamidine. The mechanisms of action of melarsoprol and of drug resistance are complex and have been the subjects of considerable study.[88,89,102] The metabolism of trypanothione appears to be a central effect of the drug on the parasite. Melarsoprol interacts with thiol groups of several key proteins, depriving the parasite of its main sulfhydryl antioxidant and inhibiting trypanothione reductase, also depriving the parasite of the essential enzyme system that is responsible for keeping trypanothione reduced.[97] Melarsoprol enters the parasite via an adenosine transporter, and resistant strains lack this transport system.[107]

Melarsoprol can only be given IV. Penetration into the brain and CSF is low but sufficient for activity because of the drug's high trypanocidal activity. Melarsoprol is rapidly transformed into active metabolites in plasma, with the parent drug having a half-life of less than 30 minutes.[108] Melarsen oxide is the predominant active metabolite, and it is excreted rapidly, with about 80% of the arsenic found in feces.[109]

There are no pharmacokinetic data on melarsoprol distribution and metabolism in patients with renal or liver disease, obesity, or ascites regarding dose adjustments in these settings. Melarsoprol has no known effect on pregnancy.

Melarsoprol is an extremely toxic drug. The most serious adverse reaction of melarsoprol is reactive encephalopathy, which typically develops within 4 days of the start of therapy and affects about 6% of treated patients.[110,111] The mortality of melarsoprol-induced reactive encephalopathy may be as high as 50%. Glucocorticoids administered with melarsoprol reduce the incidence of the encephalopathy. This toxic reaction is more common in East African (5%–18%) than in West African HAT (4%–8%) patients with CSF trypanosomes than in those without and in patients with high CSF white cell counts.[112] Polyneuropathy, probably caused by a direct toxic effect of the arsenic, is seen in up to 10% of patients. It typically presents as a glove-and-stocking paresthesia that progresses proximally. Motor deficits appear and, if neglected, can progress to quadriplegia. Amelioration with thiamine suggests an interaction between toxic and nutritional factors. Other adverse effects include skin rash, tremor, abdominal pain, and fever. Melarsoprol is formulated in propylene glycol. Because this excipient is intensely irritating, care must be taken to avoid extravasation. No information is available about interactions between melarsoprol and other drugs. In the United States melarsoprol is available from the CDC Drug Service.

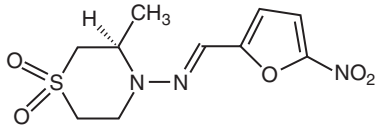

FIG. 42.6 Nifurtimox.

Nifurtimox

Nifurtimox (Lampit; Fig. 42.6) is a nitrofuran derivative that has been used for decades to treat infections with *T. cruzi*. More recently it has been found to be useful for treatment of HAT when used in combination with eflornithine, so-called NECT. The mechanism of action of nifurtimox is only partially understood and may be related to the generation of oxidative stress in trypanosomes.[113] An additional mechanism may involve reductive activation by a type I nitroreductase.[114] Nifurtimox is well absorbed orally, is metabolized in the liver, and less than 0.5% is excreted unchanged in the urine.[115]

Nifurtimox is only available in oral form. The dose is the same for all clinical stages of *T. cruzi* infection, but the recommended dosage varies as a function of age. No assays are available to determine blood levels, and no data are available to guide dose adjustments in patients with renal or hepatic insufficiency, pregnancy, or in lactating women. It is recommended that nifurtimox not be given to such patients. Resistance to nifurtimox in *T. cruzi* occurs,[116] and efforts to understand the molecular mechanisms underlying the resistance are underway.[117] The clinical significance of resistance is not known, in large measure because compliance is often uncertain, and also because confirmation of parasitologic cure after treatment is difficult. No assays are available commercially for testing *T. cruzi* for resistance to nifurtimox, and no data regarding drug-drug interactions have been published.

A sizable percentage of persons given nifurtimox develop adverse reactions.[118–120] Common GI complaints include nausea, vomiting, abdominal pain, anorexia, and weight loss. Neurologic adverse effects include restlessness, insomnia, twitching, paresthesia, seizures, and disorientation. Rashes may also occur. Factors that predispose patients to side effects have not been defined, and pretreatment protocols to reduce their occurrence have not been developed. Side effects usually resolve when the dosage is reduced or treatment is stopped. No information is available regarding the interaction of nifurtimox with other drugs. The development of malignant tumors in rabbits and mice treated with nifurtimox and related drugs is of some concern,[121] but the incidence of tumor in treated patients has not been studied.

As noted, nifurtimox is now used in combination with eflornithine for treating patients with stage 2 West African HAT. The safety and efficacy of the combined regimen, NECT, have been demonstrated.[122–124] In addition, NECT is markedly less complicated to administer and less costly compared with eflornithine monotherapy. In the United States nifurtimox is available from the CDC Drug Service.

Suramin

Suramin is a complex molecule containing eight benzene rings, with a molecular mass of 1297. It has been used to treat HAT for more than 90 years. Suramin is only used to treat the hemolymphatic form (stage 1 disease) of both East and West African trypanosomiasis. It does not penetrate the CNS to any useful degree and should never be used to treat patients with the CNS form of trypanosomiasis (stage 2 disease).

Suramin can only be given IV. It binds extensively to plasma proteins (>99%), accumulates during treatment, and is not metabolized to any great extent. It is slowly excreted in the urine, resulting in its persistence in plasma for several weeks after treatment ends.[125]

Trypanosomes take up only small amounts of suramin and do not actively concentrate the drug.[126] Resistance to suramin is uncommon, and the mechanism of resistance has not been defined.[116,127]

Treatment with suramin should be initiated at low doses that then are gradually increased. No pharmacokinetic data are available regarding the use of suramin in patients with renal or insufficiency, and no assays for monitoring blood levels are available. Given that it is excreted in the urine and is nephrotoxic, it seems prudent to reduce the dose in patients with renal insufficiency. There are no recommendations for dose reduction in liver failure. Suramin has been shown to induce abortions and to be teratogenic in animal models,[128] but no adverse effects in pregnant women have been reported, despite the long history of its use.[129]

Serious treatment-related hypotension is uncommon, occurring in only one of several thousand patients. Mild proteinuria is the most frequent adverse effect, although renal failure is rare. Thus monitoring patients for proteinuria throughout treatment is recommended. Fever occurs in approximately 10% of patients, often a few hours after infusion and may be due to reaction to breakdown products of dead trypanosomes rather than as a direct effect of the drug. Pruritus, urticaria, and stomatitis have been reported. Nausea and vomiting are uncommon if the drug is administered slowly. Optic atrophy and sensorimotor polyneuropathy have also been reported. Although suramin has activity against filarial parasites, aggravation of ocular lesions and allergic reactions has been reported in patients with onchocerciasis,[128] and the availability of ivermectin and tetracycline drugs for treatment of the *Wolbachia* endosymbiont mean that it should not be used for treatment of filariasis.

Suramin has been used in the past as therapy for cancer, albeit with doses substantially higher than those used today to treat patients with HAT. Additional adverse effects reported in such patients included corneal deposits, adrenal insufficiency, coagulopathy, neutropenia, thrombocytopenia, and fatal toxic epidermal necrolysis, but none of these effects have been observed in patients given suramin for HAT, presumably because the dosage is so much lower.

There are few data regarding interactions of suramin with other drugs. Suramin is known, however, to displace other drugs from plasma proteins, such as chlorpromazine, sulfonamides, and anticoagulants.[128] In the United States suramin is available from the CDC Drug Service.

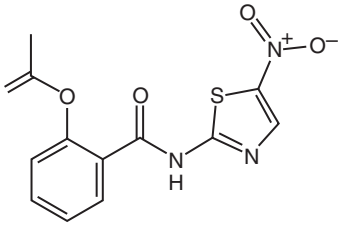

FIG. 42.7 Nitazoxanide.

Nitazoxanide

Nitazoxanide (Fig. 42.7) is a nitrothiazolyl-salicylamide derivative. The benzamide moiety resembles that of the anthelmintic drug niclosamide, whereas the nitrothiazolyl moiety resembles that of the nitroimidazole drugs tinidazole and metronidazole. It was first developed as a veterinary anthelmintic, with its activity against human tapeworms first reported in 1984.[130] Since then the drug has been shown to have activity against a wide range of pathogens, including hepatitis B and C,[131] *Clostridioides difficile* (formerly *Clostridium difficile*)[132] *Helicobacter pylori,*[133] and *Mycobacterium tuberculosis.*[134] Although clinical trials have indicated that it has activity against a broad range of intestinal protozoa and helminths,[135–138] it is approved by FDA only for treatment of giardiasis and cryptosporidiosis.

Trials in patients with cryptosporidiosis indicate that it has useful activity in HIV-negative individuals[139–141] when administered twice daily for 3 days in the following doses: 500 mg (those older than 12 years), 200 mg (children age 4–11 years), and 100 mg (children age 1–3 years). Symptom resolution is expected in 4 to 5 days, with a sustained response to treatment reported after 14 days of treatment. For cryptosporidiosis in the setting of HIV infection, the drug shows significantly inferior efficacy,[142] with randomized[143–145] and uncontrolled[141] studies indicating that prolonged therapy results in a modest-at-best response.

For giardiasis, a 3-day course of therapy, administered in the same dose as for cryptosporidiosis, reduces the duration of diarrhea and shedding of parasites. In a single-case report it cured refractory giardiasis in a patient with HIV-induced immunosuppression who had metronidazole- and albendazole-resistant giardiasis.[146] However, in an open-label, randomized, controlled trial in children, single-dose tinidazole, 50 mg/

kg, was shown to be more effective than a 3-day course of nitazoxanide administered in a dose of 7.5 mg/kg twice daily for 3 days.[147]

Nitazoxanide is active against a variety of protozoan and helminth parasites, including *E. histolytica*,[148] *Cystoisospora* (*Isospora) belli*,[149] *Blastocystis hominis*,[150] microsporidiosis,[151] and intestinal tapeworm[152] and nematode infections.[135–137] In addition, it has been shown to have activity in fascioliasis.[153] However, for all these parasites it has not shown significant superiority to other agents.

Published data indicate that nitazoxanide acts by inhibiting the activity of pyruvate-ferredoxin oxidoreductase, an enzyme essential for electron transfer and energy metabolism in anaerobic bacteria and parasites.[154] Although in vitro induction of drug resistance in *Giardia intestinalis*[155] has been reported, the mechanism of drug resistance has not been clearly defined.[156]

Nitazoxanide is available in both liquid and tablet forms; administration with food is recommended to improve bioavailability. Once absorbed the drug is rapidly deacetylated to its main active metabolite, tizoxanide, which is glucuronidated and excreted in the urine and feces.[157] When administered in the recommended doses, the peak serum concentration (C_{max}) of tizoxanide is between 10 and 17.5 µg/mL, with a half-life of 1.3 hours.[158] Although no significant drug interactions have been reported, the high level of protein binding of tizoxanide (>99%)[157] indicates a potential interaction with other drugs that also are highly protein bound. Nitazoxanide is well tolerated when administered in the recommended dose, with the rate of reported side effects no higher than placebo.[158] There are no data on dose adjustment in renal or hepatic insufficiency. Likewise, there are no data on safety in pregnancy, although reproductive toxicity studies in laboratory animals done by the manufacturer did not reveal any adverse findings.[159]

Diloxanide

Diloxanide furoate is a luminal amebicide whose primary indication is to clear *E. histolytica* cysts. Published data indicate that paromomycin is the preferred drug for this indication.[66,160] Moreover, diloxanide is not effective in amebic colitis or extraintestinal infection because it has little or no activity outside the intestinal lumen.[161]

The mechanism of action of diloxanide is unknown. It acts against trophozoites of *E. histolytica* that eventually form cysts. It has some structural similarities to chloramphenicol, suggesting that it may block protein synthesis.[162] In the gut diloxanide is hydrolyzed into diloxanide and furoic acid by bacterial and gut esterases.[163,164] It is then rapidly absorbed, glucuronidated, and excreted in the urine.[165] The unabsorbed component remains in the gut lumen as the active antiamebic agent that ultimately is excreted in the feces. Flatulence is a common adverse effect, occurring at a frequency of up to almost 90% in some studies.[166] Less common side effects include nausea, abdominal cramping, and diarrhea. The safety of diloxanide in pregnancy and lactation has not been established.

For treatment to clear passage of cysts of *E. histolytica*, after a course of metronidazole or tinidazole for treatment of invasive infection, 500 mg orally three times per day is recommended.[166,167] If required, a second course of treatment may be prescribed. A 5-day course of diloxanide with metronidazole given three times per day was shown to be efficacious in the treatment of symptomatic amebiasis, with or without dysentery. The drug can be given to children weighing more than 25 kg in a dose of 20 mg/kg in three divided doses for 10 days.[166] Doses of 25 mg/kg daily in three divided doses for 10 days have also been used.[161,168]

As noted above, for this indication paromomycin is more effective, requires a shorter duration of therapy (7 vs. 10 days), and is more widely available. Iodoquinol (diiodohydroxyquin) has also been widely used as a luminal amebicide but requires 20 days of therapy and is contraindicated in patients with hepatic impairment or allergy to iodine.[169]

Combined preparations of diloxanide furoate and metronidazole have also been shown to be effective in the treatment of giardiasis.[170] However, there is insufficient evidence to determine whether this regime is more effective than metronidazole alone.

Nitroimidazoles

The nitroimidazoles metronidazole and tinidazole (Fig. 42.8) are the drugs of choice for treatment of giardiasis, amebiasis, and trichomoniasis. The clinical pharmacology of metronidazole is discussed in detail in Chapter 28. Tinidazole is approved by the FDA for treatment of trichomoniasis, giardiasis, as well as intestinal and extraintestinal *E. histolytica* infection. Although its precise mechanism of action is unknown, available evidence indicates that it acts in a similar way as metronidazole—through nitroradicals generated by metabolism of the drug within target organism. Apart from its activity against protozoa, tinidazole, like metronidazole, has in vitro activity against anaerobic bacteria, including organisms associated with bacterial vaginosis (*Gardnerella vaginalis*, *Bacteroides* spp., and *Prevotella* spp.) and *Helicobacter pylori*.

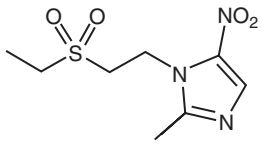

FIG. 42.8 Tinidazole.

Tinidazole is only available for oral administration, as 250- and 500-mg tablets, and as a syrup. Bioavailability is excellent, with almost complete absorption. It is metabolized in the liver by CYP3A4; it has the advantage over metronidazole of having a longer plasma half-life (12–14 hours vs. 8 hours[171]).

When administered as a single 50-mg/kg dose (maximum, 2 g), it is an effective treatment for giardiasis. In a meta-analysis of trials where single-dose (50 mg/kg) tinidazole was compared with metronidazole administered three times daily for 5 to 10 days,[172] the single-dose tinidazole regimen appeared to be more effective. However, the authors commented that the studies were small, enrolling only a total of 179 subjects, and were of low quality.

For intestinal amebiasis, a meta-analysis[173] of eight studies enrolling a total of 477 subjects, indicated that tinidazole administered in a dose of 2 g once daily for 3 days was significantly more effective than metronidazole and caused fewer adverse events. Likewise, tinidazole appeared to be at least as effective as metronidazole for treatment of amebic liver abscesses and better tolerated.[174]

For treatment of trichomoniasis, tinidazole is at least as effective as single-dose metronidazole.[175] In a meta-analysis of eight studies in which metronidazole was compared with tinidazole, although no parasitologic failures were reported, significantly higher rates of treatment and clinical failure and side effects were observed among those treated with metronidazole. Tinidazole may have a role among patients failing metronidazole therapy. In studies comparing tinidazole with metronidazole for treatment of bacterial vaginosis, similar cure rates have been reported.[176]

Reported adverse effects with tinidazole have been generally similar to those reported for metronidazole, although generally less frequent or severe. These include a metallic taste, GI disturbance (anorexia, nausea, vomiting, and epigastric discomfort), and weakness. Seizures and peripheral neuropathy have been reported with tinidazole. Tinidazole is contraindicated during the first trimester of pregnancy and in patients who are allergic to metronidazole.

Although there is a paucity of reports of drug interactions with tinidazole, the similar structure and metabolism of this drug compared with metronidazole suggests that the same precautions regarding interactions with metronidazole should be applied to tinidazole. Because tinidazole is a substrate for CYP3A4, levels of this drug may be affected by drugs that inhibit or induce this enzyme. Tinidazole shares the same propensity to interact with alcohol to cause an Antabuse-like reaction.

In summary, although there are no controlled studies comparing the efficacy of metronidazole and tinidazole for treatment of parasitic infections, tinidazole appears to be at least as effective and is better tolerated.[174] For trichomoniasis tinidazole appears to be more effective.[177] The doses of these drugs for treatment of these infections are listed in Table 42.1.

Spiramycin

Spiramycin is a macrolide antibiotic, first isolated from *Streptomyces ambofaciens*. Although its antimicrobial spectrum is similar to that of other macrolides, such as erythromycin, its principal use is for treatment

of *Toxoplasma gondii* during pregnancy or when first-line anti-*Toxoplasma* agents are inappropriate. Although it has been used for treatment of a range of bacterial infections, its use for treating the latter is limited because there are so many alternative agents. It is formulated as 250- and 500-mg capsules or tablets. Rectal and parenteral formulations are available in Europe. Spiramycin is not commercially available in the United States. It can be obtained at no cost from the Palo Alto Medical Foundation–Toxoplasma Serology Laboratory (650-853-4828), the US National Collaborative Treatment Trial Study (773-834-4152), or the FDA at 301-796-1400.

Although its mechanism of action is not fully defined, it is believed to act as an inhibitor of protein synthesis by binding to the 50S subunit of bacterial ribosomes. Like other macrolides, it is bacteriostatic.[178] Spiramycin has good bioavailability, ranging from 30% to 40%.[178] Administration away from meals is recommended because food reduces bioavailability by 50% and delays the time-to-peak serum concentration.[179] The mean half-life after oral administration is 5.5 to 8.0 hours, and the C_{max} is 0.4 to 1.4 mg/L after a single 1-g dose.[178] Although the drug is selectively concentrated in the placenta, reaching five times the maternal serum concentration, transfer across the placenta is incomplete, resulting in levels in the fetus approximately 50% of the corresponding maternal level. Spiramycin reaches higher concentrations in prostate, muscle, lymph nodes, and lung relative to plasma. The drug is secreted in milk (up to 200 µg/mL). Because the drug does not cross the blood-brain barrier, spiramycin should not be used to treat *Toxoplasma* encephalitis.[180]

Reported side effects of spiramycin include pseudomembranous colitis, cholestatic hepatitis,[181] QT prolongation with dysrhythmia,[182] thrombocytopenia,[183] and hemolysis in glucose-6-phosphate dehydrogenase–deficient patients.[184] Spiramycin has not been shown to be teratogenic and has been safely administered to pregnant women. Excretion is predominantly through the biliary route, with some enterohepatic recirculation. The drug is free of significant drug interactions. Unlike erythromycin, it does not induce cytochrome P450 enzymes. It has been reported to prolong the elimination half-life of L-dopa and carbidopa in healthy volunteers, possibly because of effects on intestinal motility that are well-known effects of macrolides.[185]

As for other macrolides, GI side effects, including nausea, vomiting, and abdominal pain, are common, particularly in high doses. On occasion, skin rashes and pruritus, including urticaria, may occur. Hypersensitivity to spiramycin has been described.[186] Of interest, although cross-sensitivity by skin prick test to other macrolides (erythromycin and clarithromycin) has been observed, oral therapy with these drugs was well tolerated. Nevertheless, it should be used with caution in patients with a history of macrolide hypersensitivity.

The utility of spiramycin in pregnancy rests on the fact that there is a delay between maternal *Toxoplasma* infection, placentitis, and then fetal infection. Thus the goal of spiramycin therapy is to prevent rather than treat fetal infection.[187] Once fetal infection is established, pyrimethamine-sulfadiazine should be used. The recommended dose of spiramycin for prevention of fetal infection (placental prophylaxis) is 1 g three times daily in the first trimester. Uncontrolled studies have shown that spiramycin therapy in newly infected pregnant women reduces transmission by up to 68% in the first trimester, 65% in the second trimester, and 32% in the third trimester.[188–190] Details of the management of infection during pregnancy are available in Chapter 278.

Because the rate of fetal infection rises with each trimester and the apparent effect of spiramycin falls, pyrimethamine and sulfadiazine are generally added later in pregnancy. Ethical considerations have made it difficult to do controlled studies of the efficacy of spiramycin in preventing transmission of *Toxoplasma* from mother to fetus. A meta-analysis published in 2007 was not able to confirm a significant reduction in transmission resulting from spiramycin therapy,[191] possibly because of the small size of the studies and the lack of an untreated control group. A nonrandomized comparative study of 255 live-born prenatally infected infants demonstrated a significant reduction in fetal transmission with treatment initiated within 4 weeks of maternal infection, whether spiramycin or sulfadiazine plus pyrimethamine was used, compared with no treatment.[192] Two recent studies also support the use of monthly screening during pregnancy and treatment of acute toxoplasmosis. In one study it was shown that monthly screening of pregnant women for *Toxoplasma* infection, followed by standard treatment of those found to be infected, was significantly more effective in reducing the rate of vertical transmission than screening every 3 months (29.5%–23.9%).[193] In a nonrandomized study comparing infected neonates who had been diagnosed and treated as a result of prenatal screening with those who have been diagnosed as a result of postnatal screening (untreated), the use of prenatal treatment, including the use of spiramycin for acutely infected women and sulfadiazine plus pyrimethamine when fetal infection was suspected or diagnosed, was associated with a significant decrease in severe neurologic sequelae or death in the neonate.[194]

In an additional nonrandomized study in which 44 patients with *Toxoplasma* chorioretinitis were treated with spiramycin alone or with sulfadiazine plus pyrimethamine, no difference in efficacy between the two groups was observed, but subjects in the spiramycin arm had fewer side effects. Hence spiramycin may be an alternative if standard therapy cannot be tolerated.[195]

Atovaquone

Originally developed as an antimalarial agent on the basis of potent in vitro activity against drug-resistant strains of *Plasmodium falciparum*, this hydroxynaphthoquinone was subsequently found to be active against a number of other microorganisms, including *P. jirovecii*, *T. gondii*, *Babesia microti*, *Cryptosporidium parvum*, *Encephalitozoon intestinalis*, *L. donovani*, *E. histolytica*, and *Trichomonas vaginalis*. Toxoplasmosis and babesiosis can be effectively treated with atovaquone when used in combination with pyrimethamine and azithromycin, respectively. See Chapter 41 for discussion of the pharmacology of this drug.

OTHER DRUGS RARELY USED TO TREAT INTESTINAL PROTOZOAL INFECTIONS

A number of other luminal antiprotozoal agents active against *E. histolytica* and *G. intestinalis* are now rarely used in most settings because of the availability of more active, more easily administered, and less toxic alternatives. These include iodoquinol, also known as diiodohydroxyquin; a halogenated 8-hydroxyquinolone, quinacrine, also known as mecaprine; emetine; and dehydroemetine. None of these drugs is readily available, but they can be obtained in the United States from the CDC Drug Service.

Key References

The complete reference list is available online at Expert Consult.

4. Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis*. 2016;63:e202–e264.
7. Wortmann G, Zapor M, Ressner R, et al. Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg*. 2010;83:1028–1033.
8. Sundar S, Chakravarty J, Agarwal D, et al. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N Engl J Med*. 2010;362:504–512.
17. Haldar AK, Sen P, Roy S. Use of antimony in the treatment of leishmaniasis: current status and future directions. *Mol Biol Int*. 2011;2011:571242.
30. Gasser RA Jr, Magill AJ, Oster CN, et al. Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis*. 1994;18:83–90.
35. Monge-Maillo B, Lopez-Velez R. Therapeutic options for Old World cutaneous leishmaniasis and New World cutaneous and mucocutaneous leishmaniasis. *Drugs*. 2013;73:1889–1920.
36. Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med*. 2002;347:1739–1746.
49. Dorlo TPC, Balasegaram M, Beijnen JH, et al. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *J Antimicrob Chemother*. 2012;67:2576–2597.
50. Dorlo TPC, van Thiel PPAM, Huitema ADR, et al. Pharmacokinetics of miltefosine in Old World cutaneous leishmaniasis patients. *Antimicrob Agents Chemother*. 2008;52:2855–2860.
51. Oliveira LF, Schubach AO, Martins MM, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. *Acta Trop*. 2011;118:87–96.
52. van Thiel PPAM, Leenstra T, Kager PA, et al. Miltefosine treatment of *Leishmania major* infection: an observational study involving Dutch military personnel returning from northern Afghanistan. *Clin Infect Dis*. 2010;50:80–83.
54. Davidson RN, den Boer M, Ritmeijer K. Paromomycin. *Trans R Soc Trop Med Hyg*. 2009;103:653–660.
60. Kim DH, Chung HJ, Bleys J, et al. Is paromomycin an effective and safe treatment against cutaneous leishmaniasis? A meta-analysis of 14 randomized controlled trials. *PLoS Negl Trop Dis*. 2009;3:e381.

61. Ben Salah A, Ben Messaoud N, Guedri E, et al. Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. *N Engl J Med*. 2013;368:524–532.
66. Blessmann J, Tannich E. Treatment of asymptomatic intestinal *Entamoeba histolytica* infection. *N Engl J Med*. 2002;347:1384.
67. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trial Group. *Clin Infect Dis*. 2000;31:1084–1092.
68. Smith NH, Cron S, Valdez LM, et al. Combination drug therapy for cryptosporidiosis in AIDS. *J Infect Dis*. 1998;178:900–903.
75. Conte JE Jr. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. *J Infect Dis*. 1991;163:169–175.
78. Munday JC, Eze AA, Baker N, et al. *Trypanosoma brucei* aquaglyceroporin 2 is a high-affinity transporter for pentamidine and melaminophenyl arsenic drugs and the main genetic determinant of resistance to these drugs. *J Antimicrob Chemother*. 2014;69:651–663.
85. Soy D, Aldasoro E, Guerrero L, et al. Population pharmacokinetics of benznidazole in adult patients with Chagas disease. *Antimicrob Agents Chemother*. 2015;59:3342–3349.
86. Wiens MO, Kanters S, Mills E, et al. Systematic review and meta-analysis of the pharmacokinetics of benznidazole in the treatment of Chagas disease. *Antimicrob Agents Chemother*. 2016;60:7035–7042.
96. Mesu V, Kalonji WM, Bardonneau C, et al. Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *Lancet*. 2018;391:144–154.
100. Vincent IM, Creek D, Watson DG, et al. A molecular mechanism for eflornithine resistance in African trypanosomes. *PLoS Pathog*. 2010;6:e1001204.
103. Milord F, Pepin J, Loko L, et al. Efficacy and toxicity of eflornithine for treatment of *Trypanosoma brucei gambiense* sleeping sickness. *Lancet*. 1992;340:652–655.
106. Barrett MP, Vincent IM, Burchmore RJ, et al. Drug resistance in human African trypanosomiasis. *Future Microbiol*. 2011;6:1037–1047.
107. Carter NS, Fairlamb AH. Arsenical-resistant trypanosomes lack an unusual adenosine transporter. *Nature*. 1993;361:173–176.
112. Pepin J, Milord F, Khonde AN, et al. Risk factors for encephalopathy and mortality during melarsoprol treatment of *Trypanosoma brucei gambiense* sleeping sickness. *Trans R Soc Trop Med Hyg*. 1995;89:92–97.
119. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. *N Engl J Med*. 2011;364:2527–2534.
122. Schmid C, Kuemmerle A, Blum J, et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for *T. b. gambiense* sleeping sickness. *PLoS Negl Trop Dis*. 2012;6:e1920.
123. Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet*. 2009;374:56–64.
124. Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage human African trypanosomiasis. *Cochrane Database Syst Rev*. 2013;(6):CD006201.
138. Ochoa TJ, White AC Jr. Nitazoxanide for treatment of intestinal parasites in children. *Pediatr Infect Dis J*. 2005;24:641–642.
139. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis*. 2001;184:103–106.
140. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet*. 2002;360:1375–1380.
142. Cabada MM, White AC Jr. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis*. 2010;23:494–499.
144. Amadi B, Mwiya M, Sianongo S, et al. High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect Dis*. 2009;9:195.
146. 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*. 2001;32:1792–1794.
148. Rossignol JF, Kabil SM, El-Gohary Y, et al. Nitazoxanide in the treatment of amoebiasis. *Trans R Soc Trop Med Hyg*. 2007;101:1025–1031.
161. Botero D. Treatment of acute and chronic intestinal amoebiasis with entamide furoate. *Trans R Soc Trop Med Hyg*. 1964;58:419–421.
168. Rubidge CJ, Scragg JN, Powell SJ. Treatment of children with acute amoebic dysentery. Comparative trial of metronidazole against a combination of dehydroemetine, tetracycline, and diloxanide furoate. *Arch Dis Child*. 1970;45:196–197.
171. Lamp KC, Freeman CD, Klutman NE, et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet*. 1999;36:353–373.
172. Granados CE, Reveiz L, Uribe LG, et al. Drugs for treating giardiasis. *Cochrane Database Syst Rev*. 2012;(12):CD007787.
173. Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. *Cochrane Database Syst Rev*. 2009;(2):CD006085.
174. Tinidazole (Tindamax)—a new anti-protozoal drug. *Med Lett Drugs Ther*. 2004;46:70–72.
178. Rubinstein E, Keller N. Spiramycin renaissance. *J Antimicrob Chemother*. 1998;42:572–576.
189. Forestier F, Daffos F, Hohlfeld P, et al. Infectious fetal diseases. Prevention, prenatal diagnosis, practical measures. *Presse Med*. 1991;20:1448–1454.
190. Couvreur J, Desmonts G, Thulliez P. Prophylaxis of congenital toxoplasmosis. Effects of spiramycin on placental infection. *J Antimicrob Chemother*. 1988;22(supplB):193–200.
192. Gras L, Wallon M, Pollak A, et al. Association between prenatal treatment and clinical manifestations of congenital toxoplasmosis in infancy: a cohort study in 13 European centres. *Acta Paediatr*. 2005;94:1721–1731.
193. Wallon M, Peyron F, Cornu C, et al. Congenital *Toxoplasma* infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. *Clin Infect Dis*. 2013;56:1223–1231.

References

1. Lemke A, Kiderlen AF, Kayser O. Amphotericin B. *Appl Microbiol Biotechnol*. 2005;68:151–162.
2. Ramos H, Valdivieso E, Gamargo M, et al. Amphotericin B kills unicellular leishmanias by forming aqueous pores permeable to small cations and anions. *J Membr Biol*. 1996;152:65–75.
3. Mwenechanya R, Kovarova J, Dickens NJ, et al. Sterol 14alpha-demethylase mutation leads to amphotericin B resistance in *Leishmania mexicana*. *PLoS Negl Trop Dis*. 2017;11:e0005649.
4. Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis*. 2016;63: e202–e264.
5. Solomon M, Pavlotzky F, Barzilai A, et al. Liposomal amphotericin B in comparison to sodium stibogluconate for *Leishmania braziliensis* cutaneous leishmaniasis in travelers. *J Am Acad Dermatol*. 2013;68:284–289.
6. Cunha MA, Leao AC, de Cassia Soler R, et al. Efficacy and safety of liposomal amphotericin B for the treatment of mucosal leishmaniasis from the New World: a retrospective study. *Am J Trop Med Hyg*. 2015;93:1214–1218.
7. Wortmann G, Zapor M, Ressner R, et al. Lipsosomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg*. 2010;83:1028–1033.
8. Sundar S, Chakravarty J, Agarwal D, et al. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N Engl J Med*. 2010;362:504–512.
9. Pandey K, Pal B, Siddiqui NA, et al. Efficacy and safety of liposomal amphotericin B for visceral leishmaniasis in children and adolescents at a tertiary care center in Bihar, India. *Am J Trop Med Hyg*. 2017;97:1498–1502.
10. Goodwin LG. Pentostam (sodium stibogluconate); a 50-year personal reminiscence. *Trans R Soc Trop Med Hyg*. 1995;89:339–341.
11. Frézard F, Martins PS, Barbosa MCM, et al. New insights into the chemical structure and composition of the pentavalent antimonial drugs, meglumine antimonate and sodium stibogluconate. *J Inorg Biochem*. 2008;102:656–665.
12. Berman JD, Edwards N, King M, et al. Biochemistry of Pentostam resistant *Leishmania*. *Am J Trop Med Hyg*. 1989;40:159–164.
13. Berman JD, Gallalee JV, Best JM. Sodium stibogluconate (Pentostam) inhibition of glucose catabolism via the glycolytic pathway, and fatty acid beta-oxidation in *Leishmania mexicana* amastigotes. *Biochem Pharmacol*. 1987;36:197–201.
14. Cunningham ML, Fairlamb AH. Trypanothione reductase from *Leishmania donovani*. Purification, characterisation and inhibition by trivalent antimonials. *Eur J Biochem*. 1995;230:460–468.
15. Walker J, Saravia NG. Inhibition of *Leishmania donovani* promastigote DNA topoisomerase I and human monocyte DNA topoisomerases I and II by antimonial drugs and classical antitopoisomerase agents. *J Parasitol*. 2004;90:1155–1162.
16. Demicheli C, Frézard F, Mangrum JB, et al. Interaction of trivalent antimony with a CCHC zinc finger domain: potential relevance to the mechanism of action of antimonial drugs. *Chem Commun (Camb)*. 2008;39:4828–4830.
17. Haldar AK, Sen P, Roy S. Use of antimony in the treatment of leishmaniasis: current status and future directions. *Mol Biol Int*. 2011;2011:571242.
18. Murray HW, Nathan CF. Macrophage microbicidal mechanisms in vivo: reactive nitrogen versus oxygen intermediates in the killing of intracellular visceral *Leishmania donovani*. *J Exp Med*. 1999;189:741–746.
19. Liew FY, Millott S, Parkinson C, et al. Macrophage killing of *Leishmania* parasite in vivo is mediated by nitric oxide from L-arginine. *J Immunol*. 1990;144:4794–4797.
20. Dasgupta B, Roychoudhury K, Ganguly S, et al. Antileishmanial drugs cause up-regulation of interferon-gamma receptor 1, not only in the monocytes of visceral leishmaniasis cases but also in cultured THP1 cells. *Ann Trop Med Parasitol*. 2003;97:245–257.
21. Chakravarty J, Sundar S. Drug resistance in leishmaniasis. *J Glob Infect Dis*. 2010;2:167–176.
22. Jeddi F, Piarroux R, Mary C. Antimony resistance in *Leishmania*, focusing on experimental research. *J Trop Med*. 2011;2011.
23. Aït-Oudhia K, Gazanion E, Vergnes B, et al. *Leishmania* antimony resistance: what we know what we can learn from the field. *Parasitol Res*. 2011;109:1225–1232.
24. Perry MR, Wyllie S, Raab A, et al. Chronic exposure to arsenic in drinking water can lead to resistance to antimonial drugs in a mouse model of visceral leishmaniasis. *Proc Natl Acad Sci USA*. 2013;110:19932–19937.
25. Perry M, Wyllie S, Prajapati V, et al. Arsenic, antimony, and *Leishmania:* has arsenic contamination of drinking water in India led to treatment-resistant kala-azar? *Lancet*. 2015;385(suppl 1):S80.
26. Solomon M, Baum S, Barzilai A, et al. Treatment of cutaneous leishmaniasis with intralesional sodium stibogluconate. *J Eur Acad Dermatol Venereol*. 2009;23:1189–1192.
27. Zaghloul IY, Radwan MA, Al Jaser MH, et al. Clinical efficacy and pharmacokinetics of antimony in cutaneous leishmaniasis patients treated with sodium stibogluconate. *J Clin Pharmacol*. 2010;50:1230–1237.
28. Jaser MA, el-Yazigi A, Croft SL. Pharmacokinetics of antimony in patients treated with sodium stibogluconate for cutaneous leishmaniasis. *Pharm Res*. 1995;12:113–116.
29. Miah MT, Ayaz FM, Maniruzzaman M, et al. Kala azar in pregnancy. *Mymensingh Med J*. 2010;19:529–532.
30. Gasser RA Jr, Magill AJ, Oster CN, et al. Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis*. 1994;18:83–90.
31. Aronson NE, Wortmann GW, Byrne WR, et al. A randomized controlled trial of local heat therapy versus intravenous sodium stibogluconate for the treatment of cutaneous *Leishmania major* infection. *PLoS Negl Trop Dis*. 2010;4.
32. Wortmann GW, Aronson NE, Byrd JC, et al. Herpes zoster and lymphopenia associated with sodium stibogluconate therapy for cutaneous leishmaniasis. *Clin Infect Dis*. 1998;27:509–512.
33. Lawn SD, Armstrong M, Chilton D, et al. Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. *Trans R Soc Trop Med Hyg*. 2006;100:264–269.
34. Maheshwari A, Seth A, Kaur S, et al. Cumulative cardiac toxicity of sodium stibogluconate and amphotericin B in treatment of kala-azar. *Pediatr Infect Dis J*. 2011;30:180–181.
35. Monge-Maillo B, Lopez-Velez R. Therapeutic options for old world cutaneous leishmaniasis and New World cutaneous and mucocutaneous leishmaniasis. *Drugs*. 2013;73:1889–1920.
36. Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med*. 2002;347:1739–1746.
37. Rahman M, Ahmed B-N, Faiz MA, et al. Phase IV trial of miltefosine in adults and children for treatment of visceral leishmaniasis (kala-azar) in Bangladesh. *Am J Trop Med Hyg*. 2011;85:66–69.
38. Soto J, Toledo J, Valda L, et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. *Clin Infect Dis*. 2007;44:350–356.
39. Soto J, Rea J, Valderrama M, et al. Efficacy of extended (six weeks) treatment with miltefosine for mucosal leishmaniasis in Bolivia. *Am J Trop Med Hyg*. 2009;81:387–389.
40. Escobar P, Matu S, Marques C, et al. Sensitivities of *Leishmania* species to hexadecylphosphocholine (miltefosine), ET-18-OCH(3) (edelfosine) and amphotericin B. *Acta Trop*. 2002;81:151–157.
41. Paris C, Loiseau PM, Bories C, et al. Miltefosine induces apoptosis-like death in *Leishmania donovani* promastigotes. *Antimicrob Agents Chemother*. 2004;48:852–859.
42. Luque-Ortega JR, Rivas L. Miltefosine (hexadecylphosphocholine) inhibits cytochrome c oxidase in *Leishmania donovani* promastigotes. *Antimicrob Agents Chemother*. 2007;51:1327–1332.
43. Rakotomanga M, Loiseau PM, Saint-Pierre-Chazalet M. Hexadecylphosphocholine interaction with lipid monolayers. *Biochim Biophys Acta*. 2004;1661: 212–218.
44. Cui Z, Houweling M. Phosphatidylcholine and cell death. *Biochim Biophys Acta*. 2002;1585:87–96.
45. Ruiter GA, Zerp SF, Bartelink H, et al. Anti-cancer alkyl-lysophospholipids inhibit the phosphatidylinositol 3-kinase-Akt/PKB survival pathway. *Anticancer Drugs*. 2003;14:167–173.
46. Rakotomanga M, Blanc S, Gaudin K, et al. Miltefosine affects lipid metabolism in *Leishmania donovani* promastigotes. *Antimicrob Agents Chemother*. 2007;51:1425–1430.
47. Pérez-Victoria FJ, Sánchez-Cañete MP, Seifert K, et al. Mechanisms of experimental resistance of Leishmania to miltefosine: implications for clinical use. *Drug Resist Updat*. 2006;9:26–39.
48. Rakotomanga M, Saint-Pierre-Chazalet M, Loiseau PM. Alteration of fatty acid and sterol metabolism in miltefosine-resistant *Leishmania donovani* promastigotes and consequences for drug-membrane interactions. *Antimicrob Agents Chemother*. 2005;49:2677–2686.
49. Dorlo TPC, Balasegaram M, Beijnen JH, et al. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *J Antimicrob Chemother*. 2012;67:2576–2597.
50. Dorlo TPC, van Thiel PPAM, Huitema ADR, et al. Pharmacokinetics of miltefosine in Old World cutaneous leishmaniasis patients. *Antimicrob Agents Chemother*. 2008;52:2855–2860.
51. Oliveira LF, Schubach AO, Martins MM, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. *Acta Trop*. 2011;118: 87–96.
52. van Thiel PPAM, Leenstra T, Kager PA, et al. Miltefosine treatment of *Leishmania major* infection: an observational study involving Dutch military personnel returning from northern Afghanistan. *Clin Infect Dis*. 2010;50: 80–83.
53. Sundar S, Olliaro PL. Miltefosine in the treatment of leishmaniasis: clinical evidence for informed clinical risk management. *Ther Clin Risk Manag*. 2007;3:733–740.
54. Davidson RN, den Boer M, Ritmeijer K. Paromomycin. *Trans R Soc Trop Med Hyg*. 2009;103:653–660.
55. Jamil KM, Haque R, Rahman R, et al. Effectiveness study of paromomycin IM injection (PMIM) for the treatment of visceral leishmaniasis (VL) in Bangladesh. *PLoS Negl Trop Dis*. 2015;9:e0004118.
56. Hailu A, Musa A, Wasunna M, et al. Geographical variation in the response of visceral leishmaniasis to paromomycin in East Africa: a multicentre, open-label, randomized trial. *PLoS Negl Trop Dis*. 2010;4:e709.
57. Kimutai R, Musa AM, Njoroge S, et al. Safety and effectiveness of sodium stibogluconate and paromomycin combination for the treatment of visceral leishmaniasis in Eastern Africa: results from a pharmacovigilance programme. *Clin Drug Investig*. 2017;37:259–272.
58. Soto J, Grogl M, Berman J, et al. Limited efficacy of injectable aminosidine as single-agent therapy for Colombian cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg*. 1994;88:695–698.
59. Hepburn NC, Tidman MJ, Hunter JA. Aminosidine (paromomycin) versus sodium stibogluconate for the treatment of American cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg*. 1994;88:700–703.
60. Kim DH, Chung HJ, Bleys J, et al. Is paromomycin an effective and safe treatment against cutaneous leishmaniasis? A meta-analysis of 14 randomized controlled trials. *PLoS Negl Trop Dis*. 2009;3:e381.
61. Ben Salah A, Ben Messaoud N, Guedri E, et al. Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. *N Engl J Med*. 2013;368:524–532.
62. Sosa N, Capitan Z, Nieto J, et al. Randomized, double-blinded, phase 2 trial of WR 279,396 (paromomycin and gentamicin) for cutaneous leishmaniasis in Panama. *Am J Trop Med Hyg*. 2013;89:557–563.
63. Neal RA, Allen S, McCoy N, et al. The sensitivity of *Leishmania* species to aminosidine. *J Antimicrob Chemother*. 1995;35:577–584.
64. Maarouf M, Lawrence F, Brown S, et al. Biochemical alterations in paromomycin-treated *Leishmania donovani* promastigotes. *Parasitol Res*. 1997;83:198–202.
65. Bhandari V, Sundar S, Dujardin JC, et al. Elucidation of cellular mechanisms involved in experimental paromomycin resistance in *Leishmania donovani*. *Antimicrob Agents Chemother*. 2014;58:2580–2585.
66. Blessmann J, Tannich E. Treatment of asymptomatic intestinal *Entamoeba histolytica* infection. *N Engl J Med*. 2002;347:1384.
67. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trial Group. *Clin Infect Dis*. 2000;31:1084–1092.
68. Smith NH, Cron S, Valdez LM, et al. Combination drug therapy for cryptosporidiosis in AIDS. *J Infect Dis*. 1998;178:900–903.
69. Clark A, Hemmelgarn T, Danziger-Isakov L, et al. Intravenous pentamidine for *Pneumocystis carinii/jiroveci* pneumonia prophylaxis in pediatric transplant patients. *Pediatr Transplant*. 2015;19:326–331.
70. Huang L, Cattamanchi A, Davis JL, et al. HIV-associated *Pneumocystis* pneumonia. *Proc Am Thorac Soc*. 2011;8:294–300.
71. Mans DR, Kent AD, Hu RV, et al. Monitoring the response of patients with cutaneous leishmaniasis to treatment with pentamidine isethionate by quantitative real-time PCR, and identification of *Leishmania* parasites not responding to therapy. *Clin Exp Dermatol*. 2016;41:610–615.
72. Gadelha EP, Talhari S, Guerra JA, et al. Efficacy and safety of a single dose pentamidine (7 mg/kg) for patients with cutaneous leishmaniasis caused by *L. guyanensis:* a pilot study. *An Bras Dermatol*. 2015;90:807–813.

73. Sacher BA, Wagoner MD, Goins KM, et al. Treatment of *Acanthamoeba* keratitis with intravenous pentamidine before therapeutic keratoplasty. *Cornea*. 2015;34:49–53.
74. Jung S, Schelper RL, Visvesvara GS, et al. *Balamuthia mandrillaris* meningoencephalitis in an immunocompetent patient: an unusual clinical course and a favorable outcome. *Arch Pathol Lab Med*. 2004;128:466–468.
75. Conte JE Jr. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving hemodialysis. *J Infect Dis*. 1991;163:169–175.
76. Bronner U, Gustafsson LL, Doua F, et al. Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with *Trypanosoma gambiense* sleeping sickness. *Br J Clin Pharmacol*. 1995;39:289–295.
77. Bronner U, Doua F, Ericsson O, et al. Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of *Trypanosoma gambiense* infection in Côte d'Ivoire. *Trans R Soc Trop Med Hyg*. 1991;85:608–611.
78. Munday JC, Eze AA, Baker N, et al. *Trypanosoma brucei* aquaglyceroporin 2 is a high-affinity transporter for pentamidine and melaminophenyl arsenic drugs and the main genetic determinant of resistance to these drugs. *J Antimicrob Chemother*. 2014;69:651–663.
79. Harstad TW, Little BB, Bawdon RE, et al. Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats. *Am J Obstet Gynecol*. 1990;163:912–916.
80. Pepin J, Khonde N. Relapses following treatment of early-stage *Trypanosoma brucei gambiense* sleeping sickness with a combination of pentamidine and suramin. *Trans R Soc Trop Med Hyg*. 1996;90:183–186.
81. Thakur CP, Kumar M, Pandey AK. Comparison of regimes of treatment of antimony-resistant kala-azar patients: a randomized study. *Am J Trop Med Hyg*. 1991;45:435–441.
82. Waskin H, Stehr-Green JK, Helmick CG, et al. Risk factors for hypoglycemia associated with pentamidine therapy for *Pneumocystis* pneumonia. *JAMA*. 1988;260:345–347.
83. Comtois R, Pouliot J, Vinet B, et al. Higher pentamidine levels in AIDS patients with hypoglycemia and azotemia during treatment of *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis*. 1992;146:740–744.
84. Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. *Trop Med Int Health*. 2009;14:1064–1070.
85. Soy D, Aldasoro E, Guerrero L, et al. Population pharmacokinetics of benznidazole in adult patients with Chagas disease. *Antimicrob Agents Chemother*. 2015;59:3342–3349.
86. Wiens MO, Kanters S, Mills E, et al. Systematic review and meta-analysis of the pharmacokinetics of benznidazole in the treatment of Chagas disease. *Antimicrob Agents Chemother*. 2016;60:7035–7042.
87. Molina I, Salvador F, Sanchez-Montalva A, et al. Pharmacokinetics of benznidazole in healthy volunteers and implications in future clinical trials. *Antimicrob Agents Chemother*. 2017;61.
88. Alsford S, Kelly JM, Baker N, et al. Genetic dissection of drug resistance in trypanosomes. *Parasitology*. 2013; 1-14.
89. Alsford S, Eckert S, Baker N, et al. High-throughput decoding of antitrypanosomal drug efficacy and resistance. *Nature*. 2012;482:232–236.
90. Campos MC, Leon LL, Taylor MC, et al. Benznidazole-resistance in *Trypanosoma cruzi*: evidence that distinct mechanisms can act in concert. *Mol Biochem Parasitol*. 2014;193:17–19.
91. Pinazo MJ, Guerrero L, Posada E, et al. Benznidazole-related adverse drug reactions and their relationship to serum drug concentrations in patients with chronic Chagas disease. *Antimicrob Agents Chemother*. 2013;57:390–395.
92. Fiorelli AI, Santos RH, Oliveira JL Jr, et al. Heart transplantation in 107 cases of Chagas' disease. *Transplant Proc*. 2011;43:220–224.
93. Jennings FW, Urquhart GM. The use of the 2 substituted 5-nitroimidazole, Fexinidazole (Hoe 239) in the treatment of chronic *T. brucei* infections in mice. *Z Parasitenkd*. 1983;69:577–581.
94. Torreele E, Bourdin Trunz B, Tweats D, et al. Fexinidazole–a new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. *PLoS Negl Trop Dis*. 2010;4:e923.
95. Tarral A, Blesson S, Mordt OV, et al. Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. *Clin Pharmacokinet*. 2014;53:565–580.
96. Mesu V, Kalonji WM, Bardonneau C, et al. Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *Lancet*. 2018;391:144–154.
97. Fairlamb AH, Cerami A. Metabolism and functions of trypanothione in the Kinetoplastida. *Annu Rev Microbiol*. 1992;46:695–729.
98. Iten M, Mett H, Evans A, et al. Alterations in ornithine decarboxylase characteristics account for tolerance of *Trypanosoma brucei rhodesiense* to D,L-alpha-difluoromethylornithine. *Antimicrob Agents Chemother*. 1997;41:1922–1925.
99. Haegele KD, Alken RG, Grove J, et al. Kinetics of alpha-difluoromethylornithine: an irreversible inhibitor of ornithine decarboxylase. *Clin Pharmacol Ther*. 1981;30:210–217.
100. Vincent IM, Creek D, Watson DG, et al. A molecular mechanism for eflornithine resistance in African trypanosomes. *PLoS Pathog*. 2010;6:e1001204.
101. Baker N, Alsford S, Horn D. Genome-wide RNAi screens in African trypanosomes identify the nifurtimox activator NTR and the eflornithine transporter AAT6. *Mol Biochem Parasitol*. 2011;176:55–57.
102. Schumann Burkard G, Jutzi P, Roditi I. Genome-wide RNAi screens in bloodstream form trypanosomes identify drug transporters. *Mol Biochem Parasitol*. 2011;175:91–94.
103. Milord F, Pepin J, Loko L, et al. Efficacy and toxicity of eflornithine for treatment of *Trypanosoma brucei gambiense* sleeping sickness. *Lancet*. 1992;340: 652–655.
104. O'Toole BA, Huffman KW, Gibson JP. Effects of eflornithine hydrochloride (DFMO) on fetal development in rats and rabbits. *Teratology*. 1989;39:103–113.
105. Fairlamb AH. Future prospects for the chemotherapy of human trypanosomiasis. 1. Novel approaches to the chemotherapy of trypanosomiasis. *Trans R Soc Trop Med Hyg*. 1990;84:613–617.
106. Barrett MP, Vincent IM, Burchmore RJ, et al. Drug resistance in human African trypanosomiasis. *Future Microbiol*. 2011;6:1037–1047.
107. Carter NS, Fairlamb AH. Arsenical-resistant trypanosomes lack an unusual adenosine transporter. *Nature*. 1993;361:173–176.
108. Bronner U, Brun R, Doua F, et al. Discrepancy in plasma melarsoprol concentrations between HPLC and bioassay methods in patients with *T. gambiense* sleeping sickness indicates that melarsoprol is metabolized. *Trop Med Int Health*. 1998;3:913–917.
109. Keiser J, Ericsson O, Burri C. Investigations of the metabolites of the trypanocidal drug melarsoprol. *Clin Pharmacol Ther*. 2000;67:478–488.
110. Blum J, Nkunku S, Burri C. Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. *Trop Med Int Health*. 2001;6:390–400.
111. Blum J, Schmid C, Burri C. Clinical aspects of 2541 patients with second stage human African trypanosomiasis. *Acta Trop*. 2006;97:55–64.
112. Pepin J, Milord F, Khonde AN, et al. Risk factors for encephalopathy and mortality during melarsoprol treatment of *Trypanosoma brucei gambiense* sleeping sickness. *Trans R Soc Trop Med Hyg*. 1995;89:92–97.
113. Cerecetto H, Gonzalez M. Antiparasitic prodrug nifurtimox: revisiting its activation mechanism. *Future Microbiol*. 2011;6:847–850.
114. Hall BS, Bot C, Wilkinson SR. Nifurtimox activation by trypanosomal type I nitroreductases generates cytotoxic nitrile metabolites. *J Biol Chem*. 2011;286:13088–13095.
115. Paulos C, Paredes J, Vasquez I, et al. Pharmacokinetics of a nitrofuran compound, nifurtimox, in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol*. 1989;27:454–457.
116. Alsford S, Kelly JM, Baker N, et al. Genetic dissection of drug resistance in trypanosomes. *Parasitology*. 2013;140:1478–1491.
117. Martinez I, Nogueda B, Martinez-Hernandez F, et al. Microsatellite and mini-exon analysis of Mexican human DTU I *Trypanosoma cruzi* strains and their susceptibility to nifurtimox and benznidazole. *Vector Borne Zoonotic Dis*. 2013;13:181–187.
118. Castro JA, Diaz de Toranzo EG. Toxic effects of nifurtimox and benznidazole, two drugs used against American trypanosomiasis (Chagas' disease). *Biomed Environ Sci*. 1988;1:19–33.
119. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. *N Engl J Med*. 2011;364:2527–2534.
120. Murcia L, Carrilero B, Albajar Vinas P, et al. Nifurtimox chemotherapy: collateral effects in treated *Trypanosoma cruzi* infected patients. *Rev Esp Quimioter*. 2012;25: 74–75.
121. Teixeira AR, Calixto MA, Teixeira ML. Chagas' disease: carcinogenic activity of the antitrypanosomal nitroarenes in mice. *Mutat Res*. 1994;305:189–196.
122. Schmid C, Kuemmerle A, Blum J, et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for *T. b. gambiense* sleeping sickness. *PLoS Negl Trop Dis*. 2012;6:e1920.
123. Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet*. 2009;374:56–64.
124. Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage human African trypanosomiasis. *Cochrane Database Syst Rev*. 2013;(6):CD006201.
125. Edwards G, Breckenridge AM. Clinical pharmacokinetics of anthelmintic drugs. *Clin Pharmacokinet*. 1988;15:67–93.
126. Fairlamb AH, Bowman IB. Uptake of the trypanocidal drug suramin by bloodstream forms of *Trypanosoma brucei* and its effect on respiration and growth rate in vivo. *Mol Biochem Parasitol*. 1980;1:315–333.
127. Scott AG, Tait A, Turner CM. Characterisation of cloned lines of *Trypanosoma brucei* expressing stable resistance to MelCy and suramin. *Acta Trop*. 1996;60:251–262.
128. Hawking F. Suramin: with special reference to onchocerciasis. *Adv Pharmacol Chemother*. 1978;15:289–322.
129. Nadjm B, Van Tulleken C, Macdonald D, et al. East African trypanosomiasis in a pregnant traveler. *Emerg Infect Dis*. 2009;15:1866–1867.
130. Rossignol JF, Maisonneuve H. Nitazoxanide in the treatment of *Taenia saginata* and *Hymenolepis nana* infections. *Am J Trop Med Hyg*. 1984;33:511–512.
131. Korba BE, Montero AB, Farrar K, et al. Nitazoxanide, tizoxanide and other thiazolides are potent inhibitors of hepatitis B virus and hepatitis C virus replication. *Antiviral Res*. 2008;77:56–63.
132. McVay CS, Rolfe RD. In vitro and in vivo activities of nitazoxanide against *Clostridium difficile*. *Antimicrob Agents Chemother*. 2000;44:2254–2258.
133. Megraud F, Occhialini A, Rossignol JF. Nitazoxanide, a potential drug for eradication of *Helicobacter pylori* with no cross-resistance to metronidazole. *Antimicrob Agents Chemother*. 1998;42:2836–2840.
134. Shigyo K, Ocheretina O, Merveille YM, et al. Efficacy of nitazoxanide against clinical isolates of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2013;57:2834–2837.
135. Romero Cabello R, Guerrero LR, Munoz Garcia MR, et al. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. *Trans R Soc Trop Med Hyg*. 1997;91:701–703.
136. Davila-Gutierrez CE, Vasquez C, Trujillo-Hernandez B, et al. Nitazoxanide compared with quinfamide and mebendazole in the treatment of helminthic infections and intestinal protozoa in children. *Am J Trop Med Hyg*. 2002;66:251–254.
137. Diaz E, Mondragon J, Ramirez E, et al. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. *Am J Trop Med Hyg*. 2003;68:384–385.
138. Ochoa TJ, White AC Jr. Nitazoxanide for treatment of intestinal parasites in children. *Pediatr Infect Dis J*. 2005;24:641–642.
139. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum:* a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis*. 2001;184:103–106.
140. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet*. 2002;360:1375–1380.
141. Rossignol JF, Kabil SM, el-Gohary Y, et al. Effect of nitazoxanide in diarrhea and enteritis caused by *Cryptosporidium* species. *Clin Gastroenterol Hepatol*. 2006;4:320–324.
142. Cabada MM, White AC Jr. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis*. 2010;23:494–499.
143. Zulu I, Kelly P, Njobvu L, et al. Nitazoxanide for persistent diarrhoea in Zambian acquired immune deficiency syndrome patients: a randomized-controlled trial. *Aliment Pharmacol Ther*. 2005;21:757–763.
144. Amadi B, Mwiya M, Sianongo S, et al. High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect Dis*. 2009;9:195.
145. Rossignol JF, Hidalgo H, Feregrino M, et al. A double-'blind' placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. *Trans R Soc Trop Med Hyg*. 1998;92:663–666.

146. 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*. 2001;32:1792–1794.
147. Escobedo AA, Alvarez G, Gonzalez ME, et al. The treatment of giardiasis in children: single-dose tinidazole compared with 3 days of nitazoxanide. *Ann Trop Med Parasitol*. 2008;102:199–207.
148. Rossignol JF, Kabil SM, El-Gohary Y, et al. Nitazoxanide in the treatment of amoebiasis. *Trans R Soc Trop Med Hyg*. 2007;101:1025–1031.
149. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. *Am J Trop Med Hyg*. 1997;56:637–639.
150. Rossignol JF, Kabil SM, Said M, et al. Effect of nitazoxanide in persistent diarrhea and enteritis associated with *Blastocystis hominis*. *Clin Gastroenterol Hepatol*. 2005;3:987–991.
151. Bicart-See A, Massip P, Linas MD, et al. Successful treatment with nitazoxanide of *Enterocytozoon bieneusi* microsporidiosis in a patient with AIDS. *Antimicrob Agents Chemother*. 2000;44:167–168.
152. Lateef M, Zargar SA, Khan AR, et al. Successful treatment of niclosamide- and praziquantel-resistant beef tapeworm infection with nitazoxanide. *Int J Infect Dis*. 2008;12:80–82.
153. Favennec L, Jave Ortiz J, Gargala G, et al. Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of fascioliasis in adults and children from northern Peru. *Aliment Pharmacol Ther*. 2003;17:265–270.
154. Hoffman PS, Sisson G, Croxen MA, et al. Antiparasitic drug nitazoxanide inhibits the pyruvate oxidoreductases of *Helicobacter pylori,* selected anaerobic bacteria and parasites, and *Campylobacter jejuni*. *Antimicrob Agents Chemother*. 2007;51:868–876.
155. Muller J, Sterk M, Hemphill A, et al. Characterization of *Giardia lamblia* WB C6 clones resistant to nitazoxanide and to metronidazole. *J Antimicrob Chemother*. 2007;60:280–287.
156. Muller J, Ley S, Felger I, et al. Identification of differentially expressed genes in a *Giardia lamblia* WB C6 clone resistant to nitazoxanide and metronidazole. *J Antimicrob Chemother*. 2008;62: 72–82.
157. Broekhuysen J, Stockis A, Lins RL, et al. Nitazoxanide: pharmacokinetics and metabolism in man. *Int J Clin Pharmacol Ther*. 2000;38:387–394.
158. Stockis A, De Bruyn S, Gengler C, et al. Nitazoxanide pharmacokinetics and tolerability in man during 7 days dosing with 0.5 g and 1 g b.i.d. *Int J Clin Pharmacol Ther*. 2002;40:221–227.
159. Jones JL, Schulkin J, Maguire JH. Therapy for common parasitic diseases in pregnancy in the United States: a review and a survey of obstetrician/gynecologists' level of knowledge about these diseases. *Obstet Gynecol Surv*. 2005;60:386–393.
160. McAuley JB, Herwaldt BL, Stokes SL, et al. Diloxanide furoate for treating asymptomatic *Entamoeba histolytica* cyst passers: 14 years' experience in the United States. *Clin Infect Dis*. 1992;15:464–468.
161. Botero D. Treatment of acute and chronic intestinal amoebiasis with entamide furoate. *Trans R Soc Trop Med Hyg*. 1964;58:419–421.
162. Knight R. The chemotherapy of amoebiasis. *J Antimicrob Chemother*. 1980;6:577–593.
163. Gadkariem EA, Belal F, Abounassif MA, et al. Stability studies on diloxanide furoate: effect of pH, temperature, gastric and intestinal fluids. *Farmaco*. 2004;59:323–329.
164. Osisanya JO. Comparative in vitro activity of mefloquine, diloxanide furoate and other conventionally used amoebicides against *Entamoeba histolytica*. *East Afr Med J*. 1986;63:263–268.
165. Dubey MP, Gupta PS, Chuttani HK. Entamide furoate in the treatment of intestinal amoebiasis. *J Trop Med Hyg*. 1965;68:63–66.
166. Wolfe MS. Nondysenteric intestinal amebiasis. Treatment with diloxanide furoate. *JAMA*. 1973;224:1601–1604.
167. Ravdin JI. Amebiasis. *Clin Infect Dis*. 1995;20:1453–1464, quiz 1465–1456.
168. Rubidge CJ, Scragg JN, Powell SJ. Treatment of children with acute amoebic dysentery. Comparative trial of metronidazole against a combination of dehydroemetine, tetracycline, and diloxanide furoate. *Arch Dis Child*. 1970;45:196–197.
169. Reed SL. Amebiasis: an update. *Clin Infect Dis*. 1992;14:385–393.
170. Qureshi H, Ali A, Baqai R, et al. Efficacy of a combined diloxanide furoate-metronidazole preparation in the treatment of amoebiasis and giardiasis. *J Int Med Res*. 1997;25:167–170.
171. Lamp KC, Freeman CD, Klutman NE, et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet*. 1999;36:353–373.
172. Granados CE, Reveiz L, Uribe LG, et al. Drugs for treating giardiasis. *Cochrane Database Syst Rev*. 2012;(12):CD007787.
173. Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. *Cochrane Database Syst Rev*. 2009;(2):CD006085.
174. Tinidazole (Tindamax)—a new anti-protozoal drug. *Med Lett Drugs Ther*. 2004;46:70–72.
175. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. *Cochrane Database Syst Rev*. 2003;(2):CD000218.
176. Hager WD. Treatment of metronidazole-resistant *Trichomonas vaginalis* with tinidazole: case reports of three patients. *Sex Transm Dis*. 2004;31:343–345.
177. Bachmann LH, Hobbs MM, Sena AC, et al. *Trichomonas vaginalis* genital infections: progress and challenges. *Clin Infect Dis*. 2011;53(suppl 3):S160–S172.
178. Rubinstein E, Keller N. Spiramycin renaissance. *J Antimicrob Chemother*. 1998;42:572–576.
179. Frydman AM, Le Roux Y, Desnottes JF, et al. Pharmacokinetics of spiramycin in man. *J Antimicrob Chemother*. 1988;22(supplB):93–103.
180. Ruf B, Pohle HD. Role of clindamycin in the treatment of acute toxoplasmosis of the central nervous system. *Eur J Clin Microbiol Infect Dis*. 1991;10:183–186.
181. Saab YB, Mroueh MA. Spiramycin-induced liver injury. *Ann Pharmacother*. 2002;36:1972.
182. Stramba-Badiale M, Nador F, Porta N, et al. QT interval prolongation and risk of life-threatening arrhythmias during toxoplasmosis prophylaxis with spiramycin in neonates. *Am Heart J*. 1997;133:108–111.
183. Buhl MR, White JM. Spiramycin-induced thrombocytopenia in a HIV-infected patient. *Scand J Infect Dis*. 1992;24:115.
184. Sarma PS. Oxidative haemolysis after spiramycin. *Postgrad Med J*. 1997;73:686–687.
185. Brion N, Kollenbach K, Marion MH, et al. Effect of a macrolide (spiramycin) on the pharmacokinetics of L-dopa and carbidopa in healthy volunteers. *Clin Neuropharmacol*. 1992;15:229–235.
186. Sanchez-Morillas L, Laguna-Martinez JJ, Reano-Martos M, et al. Hypersensitivity to spiramycin with good tolerance of other macrolides. *J Investig Allergol Clin Immunol*. 2007;17:417–418.
187. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2008;47:554–566.
188. Desmonts G, Couvreur J. Congenital toxoplasmosis: a prospective study of the offspring of 542 women who acquired toxoplasmosis during pregnancy: pathophysiology of congenital disease. Paper presented at Perinatal medicine, Sixth European Congress, Vienna. Stuttgart. Georg Thieme 1979.
189. Forestier F, Daffos F, Hohlfeld P, et al. Infectious fetal diseases. Prevention, prenatal diagnosis, practical measures. *Presse Med*. 1991;20:1448–1454.
190. Couvreur J, Desmonts G, Thulliez P. Prophylaxis of congenital toxoplasmosis. Effects of spiramycin on placental infection. *J Antimicrob Chemother*. 1988;22(supplB):193–200.
191. Thiebaut R, Leproust S, Chene G, et al. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet*. 2007;369:115–122.
192. Gras L, Wallon M, Pollak A, et al. Association between prenatal treatment and clinical manifestations of congenital toxoplasmosis in infancy: a cohort study in 13 European centres. *Acta Paediatr*. 2005;94: 1721–1731.
193. Wallon M, Peyron F, Cornu C, et al. Congenital *Toxoplasma* infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years. *Clin Infect Dis*. 2013;56:1223–1231.
194. Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med*. 2010;7.
195. Hacker M, Richter R, Gumbel H, et al. Toxoplasmosis retinochorioiditis, a therapy comparison between spiramycin and pyrimethamine/sulfadiazine. *Klin Monbl Augenheilkd*. 1998;212:84–87.

43 Drugs for Helminths

James S. McCarthy and Thomas A. Moore

SHORT VIEW SUMMARY

- This chapter includes anthelmintic drugs—drugs to treat infections with roundworms (nematodes) and flatworms, with the latter subdivided into flukes (trematodes) and tapeworms (cestodes). The drugs of choice for these are listed in this summary. Alternative drugs are given in this chapter and in the chapter describing the relevant parasite. Doses are given in Table 43.1 and in the text.

INTESTINAL ROUNDWORMS

- For ascariasis, capillariasis, hookworm (*Necator* and *Ancylostoma* spp.), pinworm *(Enterobius),* and whipworm *(Trichuris),* albendazole is generally the drug of choice, with mebendazole being an alternative.
- For strongyloidiasis, ivermectin is the drug of choice.

TISSUE ROUNDWORMS

- Filariasis
  - For lymphatic filariasis caused by *Wuchereria bancrofti* and *Brugia malayi,* diethylcarbamazine or ivermectin is used.
  - For loaiasis, caused by *Loa loa,* diethylcarbamazine is the drug of choice, with the caveat that posttreatment reactions need to be avoided in high-grade microfilaremia.
  - For onchocerciasis, ivermectin is the drug of choice, potentially followed by doxycycline for its anti-*Wolbachia* effect. Caution is also advised in onchocerciasis if high-grade *L. loa* microfilaremia coexists.
  - Treatment for *Trichinella* is supportive care with or without prednisone plus albendazole.
- For flukes (*Schistosoma, Paragonimus, Clonorchis, Fasciolopsis,* and *Opisthorchis*) and intestinal cestodes (*Diphyllobothrium, Hymenolepis nana, Taenia saginata,* and *Taenia solium*), praziquantel is the drug of choice.
- The exception is *Fasciola hepatica,* for which triclabendazole is the drug of choice.
- For tissue cestodes (*Echinococcus* [hydatid disease] and cysticercosis), albendazole is the drug of choice, with dexamethasone administered in neurocysticercosis to mitigate any posttreatment reaction. Combination therapy with albendazole and praziquantel for both neurocysticercosis and hydatid disease is now commonly used.

Although a large number of drugs have been used for anthelmintic chemotherapy, treatment is dominated by three drugs—albendazole, ivermectin, and praziquantel. This is because of the generally high-level efficacy, relatively low cost, and good safety profiles of these drugs. Their spectrum of activity can be classified according to the class of helminths against which the drugs have specific efficacy: nematodes or roundworms, for which albendazole or ivermectin are generally used; flukes or trematodes, for which praziquantel is generally used; and cestodes, for which intestinal infection is generally treated with praziquantel and tissue infection with albendazole. Drug doses are given in Table 43.1.

BENZIMIDAZOLES

Since the identification in 1961 of the potent antiparasitic activity of thiabendazole, this class of drugs has played a critical role in the treatment of parasitic infections worldwide. The structure of all members of this class is based on a bicyclic ring structure where benzene and imidazole rings are fused. The separate discoveries that thiabendazole is deactivated by hydroxylation of the benzene ring and that activity is enhanced by adding a 2-methylcarbamate moiety to the imidazole ring led to the development of mebendazole and albendazole.

The principal antiparasitic effect of the benzimidazoles (with the exception of triclabendazole) appears to be through binding to β-tubulin. This prevents assembly of microtubules, resulting in disruption of cell division and energy pathways.[1,2] Interference with vital processes therefore results in parasite death. This effect on tubulin also prevents hatching in helminth eggs.[3] Its selectivity for nematodes is attributable to its 25- to 400-fold greater inhibition of nematode tubulin compared with mammalian tubulin.

With the use of albendazole in mass treatment programs, there are concerns about the continued efficacy of the benzimidazoles to treat human infections, particularly given the well-documented reports of resistance from the veterinary literature. Resistance to albendazole in veterinary nematodes is caused by a small number of single nuclear polymorphisms, resulting in amino-acid substitutions in the parasite's β-tubulin protein, the most important of which is a phenylalanine-to-tyrosine substitution at position 200, with less important changes at residues at 167 and 198.[4] Until more recently, these concerns were unsubstantiated by evidence of resistance in human isolates. However, reports suggest that benzimidazole resistance may be developing in *Wuchereria bancrofti,*[5] *Trichuris trichiura,*[4,6] and hookworms,[6,7] particularly in areas where benzimidazoles have been extensively used in lymphatic filariasis control programs. These findings portend potential threats to the future utility of benzimidazoles for treatment of helminth infections.

Albendazole

Albendazole (Fig. 43.1) has a mode of action similar to other benzimidazoles; it is effective against a wide range of helminths and some protozoa. It is directly active against intestinal parasites; thus the relatively poor absorption of the parent drug from the intestine is ideal for an intraluminal effect. For tissue-dwelling helminths, however, albendazole acts as a prodrug, with the metabolite albendazole sulfoxide being responsible for anthelmintic activity outside the intestinal lumen. The efficacy of albendazole against tissue-dwelling helminth infections such as echinococcosis is difficult to reliably predict,[8] in part because of variable levels of the active metabolite in blood and tissues.[9]

Albendazole is administered orally, either as tablets (200 mg or 400 mg) or as a suspension (2% or 4%), with the dose regimen dependent on the target parasite. Tablets may be swallowed whole, chewed, or crushed and mixed with food. The drug is poorly soluble in water, with alcohol increasing solubility. Although no studies have been undertaken in humans to investigate bioavailability and efficacy when the drug is administered with alcohol, studies in rats suggest absorption is inhibited in all but the lowest amounts.[10]

Bioavailability studies of the parent drug have not been possible because of the lack of availability of a parenteral form. An estimated

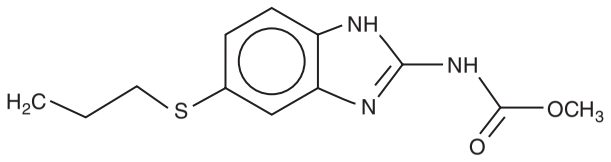

FIG. 43.1 Albendazole.

TABLE 43.1 Drugs Commonly Used for Helminth Infections

DRUG	DOSE	COMMENT
Albendazole	400 mg[a]	Taken with a fatty meal
Mebendazole	100 mg twice daily for 3 days	Less active than albendazole against extraintestinal infections
Triclabendazole	10 mg/kg once or twice	*Fasciola hepatica* infections
Pyrantel pamoate	11 mg/kg base × 1 dose; maximum dose, 1 g	
Ivermectin	150–200 µg/kg once daily × 1–2 days	
Moxidectin	8 mg PO once	Onchocerciasis
Diethylcarbamazine	6 mg/kg/day × 12 days in 3 divided doses	
Praziquantel	40/60 mg/kg/day in 1 or 2 doses × 1 day	40 mg/kg for *Schistosoma haematobium;* 60 mg/kg for *Schistosoma mansoni* and *Schistosoma japonicum*

[a]Dose varies for indication: once for ascariasis and pinworm; once daily for 3 days for hookworm and whipworm; twice daily for 7 days for strongyloidiasis, for 8–30 days for neurocysticercosis, and for 1–6 months for echinococcosis.
PO, Per os (orally).

5% to 10% of the drug is absorbed after oral administration. Once absorbed, the drug undergoes nearly complete first-pass metabolism either in the gut mucosa or in the liver to the active metabolite albendazole sulfoxide, a mixture of R(+) and S(−) enantiomers. Albendazole sulfoxide is then subject to biotransformation by cytochrome P-450 enzymes (primarily CYP3A4)[11] into the inactive metabolite albendazole sulfone.[12] The proportion of enantiomer production is species dependent, but in humans the R(+) enantiomer predominates.[13] In patients with neurocysticercosis, albendazole R(+) sulfoxide accumulates in the cerebrospinal fluid at a higher level than the S(−) enantiomer.[14] Data indicate that the R(+) enantiomer is more active than the S(−) enantiomer against *Taenia solium.*[15]

The pharmacokinetic profile of albendazole differs between men and women. For the main metabolites, albendazole sulfoxide and albendazole sulfone, there is no significant difference in half-life, time to reach peak concentration, and mean residence time. However, the apparent oral clearance and apparent distribution volume are lower in women, and the serum peak concentration (C_{max}), serum concentration-time curve (area under curve [AUC]), and area under the first-moment curve are lower in men.[16]

Food enhances the oral bioavailability of albendazole, presumably by stimulating gastric acid secretion, because albendazole absorption is pH dependent. This is true in both healthy patients[17,18] and subjects infected with tissue cestodes.[19,20] Plasma concentrations of albendazole sulfoxide are up to 5-fold higher when albendazole is administered with a fatty meal (fat content ≈ 40 g) compared with the fasting state. The administration of a single 10-mg/kg oral dose of albendazole with a high-fat meal (57 g fat, 1399 kcal) has been shown to increase the mean C_{max} and AUC by 6.5-fold and 9.4-fold, respectively.[21] The time to reach C_{max} increased from 2.5 to 5.3 hours compared with the fasting state and administration with water. The elimination half-life was not affected.

Tissue and blood concentrations of albendazole are also determined by mucosal cytochrome P-450 enzymes, which metabolize the drug, and by P-glycoprotein (Pgp), which acts as an efflux pump into the intestinal lumen.[22] In studies of patients with *Echinococcus granulosus* infection, albendazole administered orally in a dose of 10 to 14 mg/kg/day resulted in stable plasma concentrations of albendazole sulfoxide after 2 to 4 days of treatment. Significant quantities of this metabolite are measurable in lung and liver tissues and in hydatid cyst fluid obtained at surgery.[23,24] This active metabolite is excreted in bile. Albendazole sulfoxide crosses the blood-brain barrier to achieve levels in the cerebrospinal fluid approximately 43% of plasma levels.[25] However, there is significant interindividual variation because of differences in drug handling that are influenced by age, sex, or inflammation in the subarachnoid space. The high efficacy of albendazole for treatment of neurocysticercosis is most likely due to penetration of the central nervous system (CNS) by albendazole sulfoxide, which reaches higher brain levels than that achieved in plasma.[14]

Albendazole is generally taken as a single dose of 400 mg for mass drug administration for intestinal nematode infections in adults and children older than 2 years. However, apart from ascariasis, single-dose therapy, although it reduces infection intensity, is not curative. The drug has not been fully evaluated in infants, but in one study of children 9 to 23 months of age, no adverse laboratory abnormalities were noted.[26] Albendazole is mostly metabolized by the liver; thus no renal dose adjustments are needed. Conversely, absorption of albendazole and clearance of albendazole sulfoxide are delayed in patients with echinococcosis and significant biliary obstruction. However, a paucity of data limit dosing recommendations in this group.[27] The maximum recommended dose in humans, regardless of total body weight, is 800 mg/day.

In humans, single-dose albendazole therapy is very well tolerated, with an overall frequency of side effects attributable to the drug to be less than 1%.[28] In a large placebo-controlled study comprising 700 patients, the incidence of side effects in both groups was equivalent.[29] It is important to note that it is difficult to reliably differentiate symptoms attributable to the drug itself from the immune response to antigen released from dead parasites. In an analysis of clinical trials in which patients with lymphatic filariasis were administered albendazole alone or in combination with other agents, side effects were almost exclusively limited to patients with microfilaremia.[28]

Liver function abnormalities and bone marrow toxicity have been observed during prolonged courses of therapy given for treatment of echinococcosis.[28] These observations led to the initial recommendation that the drug be administered in treatment cycles of 28 days on/14 days off when prolonged use is anticipated. With increased experience, there is now less concern about continuous treatment, but monitoring is recommended.[30] The most commonly encountered side effects have been transient liver function abnormalities (≤20%) and alopecia (5%).[31] Bone marrow toxicity is rarely observed but can be irreversible. Abnormalities in liver function tests are typically less than five times the upper limit of normal and generally return to normal without stopping treatment.

Animal studies have demonstrated that both albendazole and albendazole sulfoxide are teratogenic in rats and rabbits at doses greater than 6 mg/kg/day and 30 mg/kg/day, respectively.[32] These and other observations have led to the recommendation that albendazole not be administered during pregnancy. However, clinical trials in which single-dose albendazole therapy was administered to pregnant women with hookworm infection (treated after the first trimester) demonstrated no effect on perinatal mortality, congenital malformations, or birth weight.[33] Although a small reduction in human immunodeficiency virus (HIV) viral load was noted,[34] no effect on vertical transmission of HIV was observed.[35] Of note, the trials demonstrated an increase in childhood eczema among treated children.[33,36]

Cimetidine inhibits the absorption of albendazole through reduction of gastric acidity, yet inhibits metabolism of albendazole sulfoxide by interfering with CYP3A4 enzymes, thus prolonging the elimination half-life from 7.4 (±3.3) hours to 19.0 (±11.7) hours.[37] Grapefruit juice inhibits metabolism of albendazole at the intestinal mucosa, but drug concentrations are higher than among patients administered cimetidine.[21] Short-term administration of ritonavir, a potent CYP3A4 inhibitor, does not significantly alter the pharmacokinetic parameters of albendazole. However, long-term administration results in significant decreases in AUC and C_{max}.[38] The blood concentration of albendazole sulfoxide is increased by 50% when administered concurrently with dexamethasone.[39]

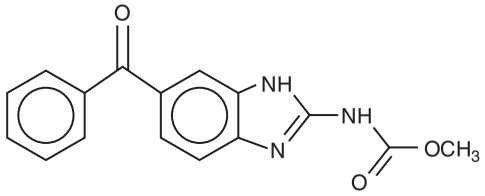

FIG. 43.2 Mebendazole.

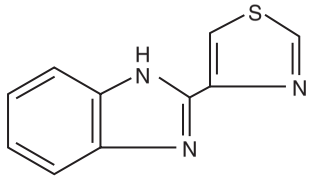

FIG. 43.3 Thiabendazole.

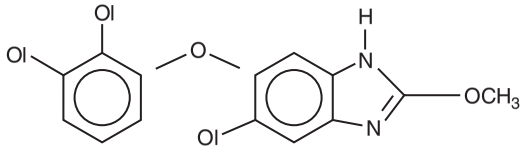

FIG. 43.4 Triclabendazole.

This has clinical relevance in the setting of treatment of neurocysticercosis, where albendazole is usually administered in conjunction with corticosteroid cover to prevent reactive cerebral edema caused by parasite death.

Mebendazole

Mebendazole (Fig. 43.2) was first introduced in 1977 as a veterinary anthelmintic agent for treatment of *Echinococcus multilocularis*. Its mode of action is similar to other benzimidazoles. Although it has been approved for the treatment of both intestinal and tissue helminths, it is less effective than albendazole for treatment of extraintestinal helminths, and therefore it is used almost exclusively for the treatment of common intestinal nematode infections.

Similar to albendazole, mebendazole is poorly soluble, is poorly absorbed, and undergoes extensive first-pass metabolism in the liver. However, it is even less well absorbed than albendazole, with a bioavailability of only 1% to 2% after administration of a single oral dose. The low bioavailability is attributable both to the low solubility of the oral formulation and to the high level of first-pass metabolism in the liver. Ingestion with fatty food increases absorption. A formulation with higher bioavailability is under development. The drug is highly protein bound (≈95%). The absorbed portion of mebendazole is predominantly metabolized by the liver. There are two major metabolites: 2-amino-5-benzoylbenzimidazole, created by amide hydrolysis, and methyl-5[α-hydroxybenzyl]-2-benzimidazole carbamate, a product of ketone reduction. In contrast to albendazole, these and other metabolites are not believed to have significant anthelmintic activity.

Mebendazole reaches its highest tissue concentrations in the liver. About half of the absorbed dose is excreted in the urine as metabolites[40]; however, a significant portion is also excreted in bile as metabolites. Mebendazole crosses the blood-brain barrier but reaches levels significantly lower than serum.

Cimetidine appears to improve the bioavailability of mebendazole.[41] Among patients with cystic echinococcosis, there is significant variability in absorption. Furthermore, concomitant administration of phenytoin and carbamazepine results in lower plasma levels, presumably because of induction of the cytochrome P-450 enzyme CYP3A4. Although no other significant drug-drug interactions have been reported with mebendazole, similar to albendazole, caution is warranted among individuals prescribed prolonged treatment courses and who are also taking medications with effects on the P-450 system.[38]

For the treatment of soil-transmitted helminths, mebendazole is typically administered as 100 mg given twice daily for 3 days. However, its pharmacokinetic profile enables a single 500-mg dose to be administered for mass treatment campaigns to control soil-transmitted helminths. Although mebendazole has not been fully evaluated in children 2 years or younger, it is well tolerated in community geohelminth control programs.[42,43] The maximum recommended dose in humans, regardless of total body weight, is 500 mg/day.

Although metabolites are excreted in the urine, there are no clinical data on the use of mebendazole in patients with kidney disease, and dose adjustment does not appear to be necessary in this setting. Nevertheless, caution seems warranted in these patients. Similarly, there are no clinical data on the use of mebendazole in patients with liver disease, but increased drug levels have been observed in a patient with cholelithiasis.[44]

When given either as a single 500-mg dose or 100 mg twice daily for 3 days, mebendazole is very well tolerated. In a trial involving more than 600 children given treatment for a geohelminth eradication program in Zanzibar, the most common adverse events were abdominal cramps (11%), fatigue (6%), headache (6%), vertigo (4.4%), and nausea (3.7%).[45] This is similar to reports from other large clinical trials. When taken at higher doses for longer periods (50 mg/kg for 3–12 months) for the treatment of echinococcosis, side effects occurred in approximately 20% of patients and were minimal and reversible in all patients without discontinuing treatment (transient elevation of transaminases, abdominal pain, headache, vertigo, urticaria, and dyspepsia).[46,47] There are also case reports of reversible bone marrow suppression.[48]

Although teratogenic in rats, the safety of mebendazole in pregnancy has been examined in three large human studies. In a survey of 170 women who took mebendazole in the first trimester of pregnancy, fetal loss or neonatal death was not significantly higher than that observed in the general population.[49] In a second series, one congenital hand malformation was observed in 112 first-trimester exposures.[49] In a larger retrospective study sponsored by the World Health Organization (WHO) involving more than 7000 Sri Lankan women who had accidentally taken the drug anytime during their pregnancy, there was a significantly lower rate of fetal loss and perinatal death, presumably resulting from reduced levels of maternal anemia.[50] Despite this ostensible beneficial effect, there was a trend toward a higher rate of congenital malformations with exposure during the first trimester (2.5% vs. 1.5%). In a randomized, placebo-controlled trial in Peru where women in the second and third trimesters were enrolled, no differences in the incidence of adverse effects were observed between the treatment arm and placebo arm.[51] The beneficial effect of decreased incidence of very low birth weight was again noted.

Thiabendazole

Although thiabendazole (Fig. 43.3) remains one of the most potent of the benzimidazoles developed, its use has dramatically declined, and it is no longer readily available. This is because thiabendazole is much less well tolerated than other equally effective agents from this class and because of the preference for ivermectin as an agent for treatment of strongyloidiasis.

Triclabendazole

Triclabendazole (Fig. 43.4) is a benzimidazole compound used routinely since 1983 in veterinary practice for the treatment of fascioliasis. It was first used for the treatment of human infection in 1986; however, its use in humans expanded in 1989 during an outbreak of fascioliasis near the Caspian Sea, when Iranian authorities approved the use of the veterinary formulation to treat human infections. In 1997 after the remarkable success of clinical trials using triclabendazole for the treatment of fascioliasis and paragonimiasis, WHO recommended that the drug be placed on the Essential Drugs List. Although the US Food and Drug Administration (FDA) has not approved triclabendazole for use in humans, it is registered in some countries where fascioliasis is endemic.

Triclabendazole is a narrow-spectrum agent and is unique among benzimidazoles in its highly specific activity against *Fasciola* spp. and

Paragonimus spp., with minimal activity against nematodes, cestodes, or other trematodes. Similar to other benzimidazoles, the mechanism of action of triclabendazole results from inhibition of microtubule formation.[52] The β-tubulin protein of *Fasciola hepatica* exhibits species-specific protein changes at position 82 (glutamic acid) and position 91 (threonine), which are unique among nematodes and cestodes. These substitutions appear to cause the fluke β-tubulin to adopt a three-dimensional structure that is relatively unaccommodating to other benzimidazoles, which are flat or L-shaped.[53] Triclabendazole exhibits a nonplanar U-shaped configuration that appears to be uniquely suited to binding to fluke β-tubulin.[52] In addition, triclabendazole-sulfoxide, the active metabolite of triclabendazole, has been shown to disrupt the tegument of both mature and immature stages of *F. hepatica*.[54] Furthermore, it is also a potent inhibitor of protein synthesis.[55]

Resistance to triclabendazole in veterinary use has become widespread since its original description in Australia.[56] A report of apparent triclabendazole-resistant *Fasciola* human infection in The Netherlands is important because of its epidemiologic relationship to resistance in livestock.[57] Susceptibility to the drug appears to be enhanced by ketoconazole[58] and methimazole[59] among strains previously known to be resistant.

After oral ingestion, absorption of triclabendazole occurs rapidly.[60] Similar to albendazole and mebendazole, triclabendazole undergoes extensive first-pass metabolism in the liver. It is converted into the active metabolite triclabendazole sulfoxide, and then the inactive metabolite triclabendazole sulfone.[61] Both metabolites are highly protein bound (>99%).[60]

After oral administration, the parent drug cannot be detected in plasma. Food enhances absorption of triclabendazole but also shortens the elimination half-life of its metabolites.[61]

Although there are no clinical data regarding treatment of patients with renal disease, dose adjustment seems unnecessary in renal disease, given the short course of therapy and the extensive hepatic metabolism of the drug. Although dose adjustment may be necessary in patients with hepatic disease, no data exist to provide insight.

Triclabendazole appears to be remarkably safe. Adverse events, when they have occurred, have been mild; short lived; and limited to abdominal pain, headache, nausea, and fatigue.[62] Abdominal pain was reported to occur in 21.5% of patients who received triclabendazole in a dose of 5 mg/kg daily for 3 days, 6.7% receiving 10 mg/kg twice daily for 1 day, and 31.3% receiving a single dose of 10 mg/kg.[63] A trial in the Bolivian Altiplano reported similar findings.[62] The abdominal pain is transient lasting less than 5 days, is typically located in the right upper quadrant, is relieved by oral spasmolytics, and has been attributed to the expulsion of dead or dying worms from the hepatobiliary system into the intestinal tract.[61,64,65] The contention that nearly all the adverse reactions in human clinical studies can be attributed to the death of adult worms is supported by ultrasound studies that have demonstrated dilated intrahepatic bile ducts caused by transient biliary obstruction associated with expulsion of dying worms. This is further supported by evidence from clinical trials in paragonimiasis, where the only gastrointestinal (GI) side effects reported were rare episodes of diarrhea. Fever has been reported in 6.3% of patients within 4 days of treatment for paragonimiasis. There have been no reports of derangement of liver function tests, renal function, or hematologic indices attributable to triclabendazole in human clinical trials. However, laboratory studies using high doses of the drug in rats and dogs have demonstrated bone marrow depression and increased serum alkaline phosphatase. No evidence of dose-related toxicity or carcinogenicity has been observed in animals. In contrast to the other benzimidazoles, triclabendazole has not been shown to cause birth defects in animal studies. Nevertheless, there are no data regarding its safety in pregnancy. Teratogenicity has been assessed in a zebrafish model, which highlights the potential importance of the sulfoxide metabolite, present at concentrations 30 times greater than the native drug.[66] Where possible, it seems prudent to avoid use in the first trimester. Triclabendazole is known to pass into breast milk, but there are no reports of adverse events in nursing infants. No data exist regarding drug-drug interactions.

Macrocyclic Lactones

Macrocyclic lactone compounds include avermectins and milbemycins. These compounds are widely used due to their broad spectrum of activity, efficacy at low doses, and excellent safety profile (Figs. 43.5 and 43.6).

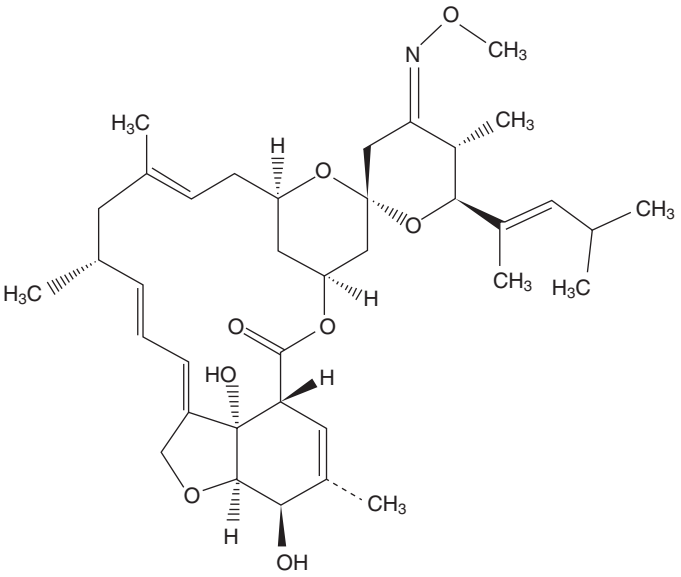

FIG. 43.6 **Moxidectin.**

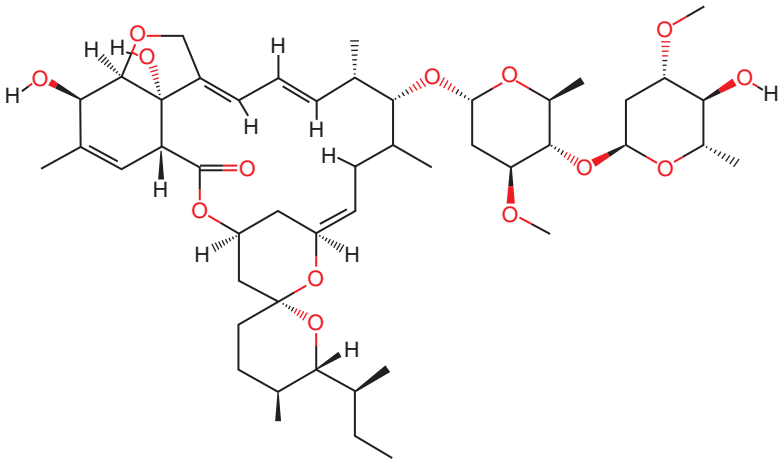

FIG. 43.5 **Ivermectin.**

Ivermectin

Ivermectin is a semisynthetic antibiotic derived from *Streptomyces avermitilis*. The organism was isolated from a soil sample taken from a golf course in Japan. Ivermectin is marketed under the brand names Stromectol (Merck, Whitehouse Station, NJ) in the United States, Mectizan (Merck) in Canada, and Ivexterm (Valeant Pharmaceuticals, Montreal, Canada) in Mexico. It is lipophilic, with poor water solubility. After the discovery of its activity against nematodes of veterinary importance, it was later found to be extremely effective against the cattle parasite *Onchocerca cervicalis;* this led to its development for treatment of onchocerciasis.[67] It is active at low doses against a wide range of helminths and ectoparasites and is the drug of choice for treatment of onchocerciasis and strongyloidiasis. It is an option for treatment of cutaneous larva migrans, head lice, and scabies. Although active against the intestinal helminths *Ascaris lumbricoides* and *Enterobius vermicularis,* it is only moderately effective in trichuriasis when given alone and has limited activity against hookworms.

Ivermectin activates neuromuscular membrane-associated chloride channels, particularly glutamate-gated channels, by binding to α-type channel subunits. The subsequent influx of chloride results in membrane hyperpolarization and muscle spasm particularly affecting the nematode pharynx, thus halting nutrient ingestion. Although ivermectin binding sites are present in the CNS of mammals, its affinity for nematode ligands is about 100 times greater than for mammals, explaining its selectivity.

Ivermectin is available for human use only as an oral formulation (either a 3-mg tablet or 6-mg scored tablet) and is generally administered as a single dose of 150 to 200 μg/kg. The bioavailability of ivermectin is increased twofold with food.[68,69] Plasma concentrations of ivermectin have been shown to decrease with ingestion of orange juice[70] and increase with ingestion of beer.[71] Its absorption half-life is approximately 1 hour.[72] The C_{max} is proportional to dose, with a value of approximately 38 to 46 μg/L reached after a therapeutic 150- to 200-μg/kg dose.[73–75] No significant differences in absorption have been found between healthy volunteers and patients with onchocerciasis. A second rise in plasma levels occurs 6 to 12 hours after ingestion, suggesting significant enterohepatic recycling.[72] Because it is a highly lipophilic drug, ivermectin is distributed widely throughout the body. Animal studies indicate that it accumulates at the highest concentration in adipose tissue and liver. Plasma protein binding is 93%.[76] The terminal half-life of the parent drug is 20 hours.[77] The elimination half-life of the metabolites of ivermectin is longer than that of the parent drug, at about 3 days.[77] It is not known whether the metabolites have antiparasitic activity. In healthy subjects, its volume of distribution is approximately 3.5 L/kg after oral administration.[78] In patients with onchocerciasis, the volume of distribution of the area was 9.9 L/kg after administration of a single 6-mg tablet.[74] The tissue distribution was similar in both groups of patients. Because of its high lipophilicity, a two-compartment model best describes its pharmacokinetic profile, with a high volume of distribution into a peripheral compartment.[79] Ivermectin is extensively metabolized in the liver by the CYP3A4 cytochrome.[80]

Ivermectin is both a substrate for the transporter Pgp[81,82] and a moderately potent Pgp inhibitor at concentrations consistent with doses used in mass treatment campaigns.[83,84] It is highly protein bound; scant pharmacokinetic and pharmacodynamic data exist regarding levels in individuals with conditions that would affect these parameters. The lack of significant macrofilaricidal activity in onchocerciasis cannot be explained by lack of penetration into onchocercal nodules, as the drug penetrates well into nodules when given as a single dose.[73] In an animal model of onchocerciasis, high concentrations were detected in the capsule wall and inside the nodule after subcutaneous administration with 500 μg/kg.[85] Because there is no significant renal handling of the drug, administration in renal failure should not be of concern. There are no data regarding safety in hepatic failure, but it is probably safe for use in this setting, given the lack of significant side effects at high doses.[68] Most of the drug is excreted in the feces as metabolites, mainly as monosaccharide derivatives; these also undergo enterohepatic recycling.[86]

In strongyloidiasis, the difficulty in achieving adequate drug levels of ivermectin in patients with disseminated strongyloidiasis and intestinal ileus can be a serious clinical problem. There is a growing experience with the use of the drug administered by subcutaneous injection of a veterinary formulation of ivermectin in the setting of ileus and disseminated strongyloidiasis.[87–89] In one report[89] in which a dose of 200 μg/kg was given every 2 days, the ivermectin level was 7.9 ng/mL 1 week after the last dose, with evidence of additional metabolite accumulation and a sustained antiparasitic effect. In another report[88] a level of 5.8 ng/mL was measured 16 hours after the first subcutaneous dose, with serum levels of 11.4 to 17.2 ng/mL being measured over the next 15 days, without evidence of significant accumulation.

Pgp appears to be important in preserving the blood-brain barrier and preventing accumulation of ivermectin in mammalian brain tissue.[90] Pgp is an essential component of the intact blood-brain barrier in vivo. In knockout mice deficient for Pgp, the 50% lethal dose of ivermectin is 100-fold lower than in wild-type mice.[81] Collies and some other breeds of dogs are unusually susceptible to neurotoxic effects of ivermectin, resulting from a mutation in the canine multidrug-resistance gene, *MDR1-1,*[91] which results in increased CNS penetration of the drug. Differences in levels of Pgp expression, protein levels, and drug passage across the gut wall and blood-brain barrier have been reported in different age groups both in laboratory animals and in human studies.[92] However, how these relate to potential CNS toxicity is uncertain, given the interspecies variations and limited data available.[93,94] It is unclear whether ivermectin is safe to use in infancy, when expression of Pgp at the blood-brain barrier is likely at its lowest levels; hence it is recommended not to administer the drug to children weighing less than 15 kg. Although not specifically studied, ivermectin has been used without dosage alteration across all ages in mass treatment campaigns. Although ivermectin use in an elderly nursing home population was reported to be associated with an increase in mortality within 6 months after treatment,[95] this report has been criticized for not controlling for comorbidities.

The successful mass distribution programs with ivermectin to control onchocerciasis have prompted the development of programs entailing coadministration with albendazole and azithromycin. The pharmacokinetic interactions of these agents have not been well studied. In a study where azithromycin, ivermectin, and albendazole were coadministered, ivermectin AUC and C_{max} were increased by 31% and 27%, respectively.[69]

Ivermectin is the drug of choice for the treatment of infection with the filarial nematode *Onchocerca volvulus*. Onchocerciasis is endemic in Central and Western Africa and until recently in certain areas of Central and South America. Administered as a single oral dose of 150 μg/kg, it has a rapid microfilaricidal effect, with most microfilariae being cleared by the end of the first week of therapy; within 1 month after treatment with ivermectin, skin microfilarial loads decrease by 95% to 99%.[96] The drug also blocks the production of new microfilariae by the adult female worms, which resume release of microfilariae 3 to 6 months after treatment.[97] This action of ivermectin to block embryonal development explains the prolonged effect in suppressing microfilariae for up to 1 year after treatment. Ivermectin also has a mild macrofilaricidal effect in reducing the longevity of the adult worms when the drug is administered every 1 to 3 months.[98,99] However, as adult *O. volvulus* worms may live up to 10 years, the drug should be administered every 6 to 12 months for the life of the adult worm.

Data indicate that a combination of ivermectin, diethylcarbamazine (DEC), and albendazole administered as a single dose for treatment of bancroftian filariasis has equivalent activity as annual therapy with ivermectin and DEC.[100]

A single dose of ivermectin is similarly microfilaricidal against *W. bancrofti*. With a single oral dose of 10 to 20 μg/kg, microfilaremia disappears for up to 3 months.[101] With higher doses (150–400 μg/kg), microfilaremia takes longer to return, and the level of parasitemia is lower than baseline.[102–104] Ivermectin appeared to be slightly inferior to DEC in producing sustained reduction of microfilaremia, even when given in combination with albendazole.[105] In lymphatic filariasis, as in onchocerciasis, ivermectin has no discernible effect on the adult worm, even when given at a dose of 4800 μg over 6 months.[106] Given these data, it is not surprising that when given as part of a mass treatment campaign, ivermectin resulted in a significantly smaller impact on hydrocele prevalence than DEC.[107,108] Nevertheless, a small trial of a triple-drug regimen with ivermectin added to standard therapy with DEC and albendazole demonstrated greater reductions in microfilaremia

with three drugs. Persistent microfilaremia was present in 11 of 12 people treated with two drugs at 1 year and none of 12 treated with three drugs, although the adverse event rates were 50% and 83%, respectively.[109]

Although the activity of ivermectin against *B. malayi* and *Brugia timori*—the less common lymphatic filarial parasites—is less well studied, it appears to be less effective against these species compared with *W. bancrofti*. Single doses of ivermectin, even as high as 400 µg/kg, result in slower clearance of microfilaremia, and this effect is shorter lived.[110] For treatment of brugian filariasis, the addition of albendazole to both DEC and ivermectin treatments did not result in improved efficacy.[111]

The effect of ivermectin against *Loa loa* appears similar to that seen in brugian filariasis. High doses of the drug (400 µg/kg) are required to clear microfilaremia,[112] and the microfilaremia clears more slowly than in bancroftian filariasis.[113] Serious adverse events, most notably fatal encephalopathy, have been reported when ivermectin was administered as part of a mass drug administration program for control of onchocerciasis in areas where loiasis was highly endemic. Although this required a temporary suspension of ivermectin distribution in these areas, mass drug administration was safely reinstituted after risk mapping tools were implemented. Serious adverse effects have been confined to individuals with high levels of microfilaremia (>30,000 microfilariae/mL); therefore ivermectin should be used with extreme caution in these patients.

A single oral dose of ivermectin resulted in sustained suppression of microfilaremia in patients infected with *Mansonella streptocerca*[114] and in a significant reduction of intensity and prevalence of infection in *Mansonella ozzardi*.[115,116] Ivermectin does not appear to be effective against *Mansonella perstans*.

Ivermectin is the drug of choice for the treatment of *Strongyloides stercoralis* infection, where administration of a single 200-µg/kg dose to children with uncomplicated infections led to a cure rate of 83%.[117] This finding is consistent with other clinical data.[118,119,120] To increase the likelihood of cure, most experts recommend an additional dose given 7 to 10 days later. Repeated courses may be needed in individuals with impaired cellular immunity, particularly patients infected with human T-cell lymphotropic virus type 1.[121] Although uncomplicated infection can be readily treated using orally administered drug, as discussed earlier, in patients with disseminated strongyloidiasis with intestinal dysfunction the drug is poorly absorbed,[87,89] and subcutaneous injection of a veterinary parenteral preparation may be required.[87,89,122,123] Ivermectin has also been given by rectal enema, but a clinical report of two cases found that clinically effective serum levels were not achieved when the drug is administered by this route.[124–126]

Ivermectin is highly effective for treatment of cutaneous larva migrans, a zoonosis usually caused by hookworms of dogs *(Ancylostoma caninum)* or cats *(Ancylostoma braziliense)*. For this indication, it is given at a dose of 150 to 200 µg/kg once daily for one or two doses.[127]

When given at a dose of 200 µg/kg/day for 2 days, ivermectin is effective for the treatment of gnathostomiasis, with a reported cure rate of 100% in one study.[128] When administered as a single dose of 200 µg/kg, cure rates range from 76% to 92%.[129] Among cases not cured, the signs of resurgent infection (as demonstrated by the recurrence of subcutaneous swelling) were not statistically significant compared with placebo.[130] The drug is reasonably well tolerated in this disease, with self-limited adverse effects that are not dose-related.[130]

Ivermectin is safe and highly effective against *A. lumbricoides*. A single dose of 100 to 200 µg/kg results in cure.[131] It is also active against pinworm caused by *E. vermicularis,* with a cure rate of up to 85% after a single oral dose ranging from 50 to 200 µg/kg.[131] However, it has limited activity in hookworm infection, with treatment resulting in reduction of worm burden but not usually cure.[131–133]

Similar to its activity against hookworm, ivermectin is relatively ineffective for the treatment of infections caused by *T. trichiura*. The cure rate after a single dose of 50 to 200 µg/kg ranges from 11% to 67%.[131,132] Higher doses[133] or extending daily treatment to 3 days[117] appears to be more effective. In this infection, combination with albendazole appears to result in a greater efficacy than when either agent is used alone.[134–136]

Although recommended as a second-line alternative to topical permethrin,[137] ivermectin is effective for the treatment of infection caused by *Sarcoptes scabiei,* in which it should be administered orally in a single dose of 200 µg/kg, with a second dose given 2 weeks later.[137,138] Ivermectin is particularly useful for treatment of crusted (Norwegian) scabies,[139] although repeated treatments are recommended. In this setting, it should be combined with a topical ascaricide, such as permethrin, alternating with keratolytic creams, such as salicylic acid or lactic acid/urea, to facilitate breakdown of the skin crusting.[137] A topical formulation of ivermectin 0.4% was approved by the FDA for control of head lice following the report of a randomized, controlled trial in which efficacy of 73.8% was reported.[140] Of note, however, short exposure intervals of body lice to sublethal amounts of ivermectin was shown to induce upregulation of detoxification genes including cytochrome P-450 monooxygenase and adenosine triphosphate–binding cassette transporter genes leading to tolerance.[141] This suggested the vulnerability of this class of drugs to the development of resistance.

Ivermectin given in the absence of helminth infection has few, if any, side effects, a fact that has permitted its use in mass drug administration programs for more than 25 years. Although high doses administered to some animals including beagle dogs and in human overdose can lead to CNS toxicity manifested by emesis, mydriasis, and ataxia, its poor penetration of the blood-brain barrier mitigates any toxic effect.[142] No significant toxicity has been reported in dose finding studies where doses as high as 2000 µg/kg, 10 times the recommended therapeutic dose, were tested.[68,143] However, as noted earlier, patients with a high parasite burden, for example, with high levels of microfilariae in the skin (onchocerciasis) or blood (lymphatic filariasis or loiasis), may have significant posttreatment reactions including postural hypotension and thus should be observed for up to 36 hours after treatment. In onchocerciasis, skin edema, pruritus, and mild eye irritation may also occur. Usually recovery follows rapidly when the patient remains recumbent, and no specific treatment is necessary. Occasionally patients require symptomatic treatment with antipyretics or antihistamines.

As noted earlier, severe complications of ivermectin therapy can occur among patients treated for onchocerciasis but with coincident heavy *L. loa* infection (>30,000 microfilariae/mL blood). A single case of hepatitis associated with ivermectin use has been reported,[144] but there are no other reports of significant immune reactions with this agent.

The use of ivermectin in mass treatment campaigns for more than 2 decades has occasionally resulted in the inadvertent administration of ivermectin to pregnant women.[145] Although no adverse effects have been recorded in retrospective studies,[146,147,148] administration of the drug in pregnancy is not advised. However, the established teratogenicity of the alternative treatment for strongyloidiasis (albendazole) suggests that ivermectin would be the drug of choice if life-threatening hyperinfection occurred in a pregnant woman. Although ivermectin reaches levels in breast milk that are about 35% of those seen in the serum, operational constraints and the absence of reports of toxicity in breastfeeding infants have resulted in a recommendation not to exclude lactating women from mass drug administration programs.[149]

Because of overuse of ivermectin as a single agent for control of parasites in cattle, resistance to ivermectin has developed in *Haemonchus contortus,* the organism for which ivermectin was originally developed as a treatment.[150] The mechanism of resistance in veterinary nematodes has not been precisely defined and may involve both target alteration and drug pumps. More than 1.3 billion tablets have been distributed in Africa, with some individuals having now received up to 20 annual treatments.[151,152] However, in some areas, this program has not resulted in interruption of transmission.[153] Reports of poor parasitologic responses to the drug[154–156] have been followed by parasitologic and epidemiologic evidence of ivermectin resistance.[157] Furthermore, in a study conducted in Cameroon, parasites obtained from individual patients demonstrated changes in the β-tubulin gene before and after the patients were treated with ivermectin.[158] Although these genetic changes developed over the 3 years the study was conducted, these parasites develop slowly, requiring about 1 year to go from birth to sexual maturity. Not surprisingly, the development of resistance to ivermectin results in resistance to related compounds such as moxidectin.[159] Exposure to increasing doses of

ivermectin is also associated with the development of cross-resistance to levamisole and pyrantel.[160]

Moxidectin

Moxidectin is a semisynthetic milbemycin macrocyclic lactone derived from the fermentation of *Streptomyces cyanogriseus* subsp. *noncyanogenus*. Nemadectin was isolated from *S. cyanogriseus* subsp. *noncyanogenus* in a soil sample in Victoria, Australia, and chemically modified by the addition of a methoxime moiety to form moxidectin.[159] Moxidectin was approved by the FDA in 2018 for use in the treatment of onchocerciasis.

Similar to ivermectin, the primary mode of action of moxidectin is believed to be via activation of glutamate gated chloride channels leading to flaccid paralysis as well as activity on related ligand gated ion channels. However, there are likely some differences in binding sites and/or mode of action, as suggested by the finding that an ivermectin-resistant strain of *Caenorhabditis elegans* demonstrates susceptibility to moxidectin.[161,162] In addition, reduced neurotoxicity in mammals of moxidectin compared with ivermectin has been observed.[163,164]

Although there have been reports of resistance to moxidectin in livestock, the resistance is not as widespread as with ivermectin, and moxidectin can often be used effectively against ivermectin-resistant parasites despite the concerns about cross-resistance. This appears in part to be due to the reduced efflux of moxidectin in Pgps[165]; however, resistance may be conferred by other genetic mutations.

Moxidectin is supplied as a pale yellow uncoated oval-shaped tablet containing 2 mg of drug. The recommended dose of moxidectin is a single dose of 8 mg (four 2-mg tablets). Moxidectin is highly lipophilic, is rapidly absorbed (2–6 hours), has a large volume of distribution, and has a very long half-life (>30 days). Administration with a high-fat meal significantly delays absorption.[166] Similar to ivermectin, moxidectin is generally well tolerated; however, like ivermectin it may cause cutaneous, ophthalmological, or systemic reactions of varying severity (Mazzotti reaction) in the treatment of onchocerciasis. These adverse reactions are due to allergic and inflammatory host responses to the death of microfilariae. There is a trend toward an increased incidence of these adverse reactions in patients with higher microfilarial burden.

Clinical trials comparing moxidectin with ivermectin in the treatment of patients with onchocerciasis revealed that some side effects occurred more frequently compared with ivermectin, presumably due to the differences in absorption and lipophilicity. Most notably, the development of symptomatic orthostatic hypotension with inability to stand without support after lying down for 5 minutes (an orthostatic hypotension provocation test) was seen in 5% of patients treated with moxidectin compared with 2% who received ivermectin. Decreases in blood pressure, which most commonly occurred on days 1 and 2 after treatment, were short-lived and alleviated when the patient lay down.[167] Patients who feel dizzy or light-headed after taking moxidectin tablets should lie down until the symptoms resolve. Patients with hyperreactive onchodermatitis (sowda) may be more likely than others to experience severe edema and worsening of onchodermatitis following the use of moxidectin.[168]

As with ivermectin, use of moxidectin in areas endemic for loiasis should be preceded by screening for microfilariae of *L. loa* to avoid the risk of acute encephalopathy. Elevation of bilirubin above the upper limit of normal occurred more often in patients treated with moxidectin than with ivermectin (2.8% vs. 0.6%). Most of the patients had single measurements of hyperbilirubinemia without concurrent elevation in transaminases. Elevation of transaminases greater than five times the upper limit of normal occurred slightly less often in patients treated with ivermectin (0.4% for alanine aminotransferase and 0.6% for aspartate aminotransferase) compared with moxidectin (1% for both alanine aminotransferase and aspartate aminotransferase).[167]

In clinical trials, no clinically significant differences in the pharmacokinetics of moxidectin were observed based on age (18–60 years old), sex, weight (42.7–107.2 kg), or mild-to-moderate renal impairment. Although the pharmacokinetic profile of moxidectin in patients with moderate-to-severe renal impairment is unknown, the fact that renal elimination of intact drug is negligible means that no reduction in the size of single-dose treatment is necessary. The effect of hepatic impairment on the pharmacokinetics of moxidectin is unknown.[169] Moxidectin is concentrated and excreted in breast milk in small quantities (0.7% of maternal dose).[170] In vitro, moxidectin is neither a substrate nor an inhibitor of CYP enzymes; in a clinical trial with midazolam, moxidectin did not alter CYP3A4 activity.[171]

Diethylcarbamazine

DEC remains the treatment of choice for lymphatic filariasis and loiasis. It can also be used for treatment of visceral larva migrans. The piperazine ring of DEC is essential for activity of the drug. Despite the description of activity of DEC against these parasites in 1940s, its mechanism of action remains poorly understood. When filarial parasites are exposed to DEC in vitro, no effect is observed. Proposed mechanisms of action include platelet-mediated triggering of the release of excretory antigen from microfilariae,[172] drug-induced alterations of prostaglandin metabolism in microfilariae and host endothelial cells resulting in immobilization due to inhibition of parasite cholinergic muscle receptors,[173,174] disruption of microtubule formation,[175] and alteration of helminth surface membranes resulting in enhanced killing by the host's immune system. Although efficacy of DEC in filariasis is variable, this has not been established to be due to resistance.

DEC is available only for oral administration. It is well absorbed, with peak plasma concentrations occurring within 1 to 2 hours. There is no significant binding to plasma proteins.[176] The drug is largely eliminated unchanged by renal excretion, with a terminal elimination half-life of 10 to 12 hours; less than 5% is excreted in feces. Alkalinization of the urine increases the half-life of the drug.[176] If more than one dose is to be administered to patients with renal impairment, the dose should be reduced commensurate with the reduction in glomerular filtration rate.[177] The pharmacokinetic profile of the drug is similar in both healthy and infected persons.[178] No data exist regarding the safety of DEC in pregnancy, but the finding of enhanced uterine contractility in rats suggests that caution is warranted.[179]

Worms can be refractory to repeated courses of therapy.[180–182] Monthly administration is known to be an effective chemoprophylactic agent for bancroftian filariasis and loiasis.[183]

Among uninfected individuals, GI upset, characterized by anorexia and nausea, is the most common side effect. Among infected patients, adverse reactions to DEC are common and proportional to the dose administered and intensity of infection. In patients with onchocerciasis, DEC can precipitate a typical side effect termed the *Mazzotti reaction,* characterized by pruritus, fever, and arthralgia.[184] The inflammatory response occurring in both the anterior (cornea) and the posterior (retina) segments of the eye can result in permanent visual damage.[185] In patients with lymphatic filariasis, similar but generally less severe systemic adverse reactions may occur, characterized by fever, headache, malaise, myalgia, and microscopic hematuria.[186] Localized effects in patients with lymphatic filariasis include pain, adenitis, lymphangitis, epididymitis, and lymphedema. As for ivermectin, life-threatening encephalitis can develop in patients with loiasis and high-burden parasitemia.[187]

DEC is active against *Ascaris* spp. Patients with ascariasis may expel live, paralyzed worms after treatment. No significant drug interactions have been reported with DEC.

Piperazine

Piperazine is a little-used anthelmintic that can be used for the treatment of ascariasis and enterobiasis. Piperazine causes an influx of chloride into nematode musculature by acting as an agonist at extrasynaptic γ-aminobutyric acid receptors. The paralyzed worm is expelled in the feces.

Doxycycline

In the past decade, it has been discovered that filarial nematodes depend on endosymbiotic bacteria of the *Wolbachia* spp. for normal development and fertility.[188] More recently, this endosymbiont has been shown to be an important determinant of the clinical manifestations of onchocerciasis[189] and has become an important drug target in patients with lymphatic filariasis.[190,191] Based on its activity against *Wolbachia,* doxycycline has

been shown to be active in onchocerciasis and lymphatic filariasis but not in loiasis because *L. loa* lacks the endosymbiont. The mechanism of action of doxycycline against *Wolbachia,* although not proven, is presumed to be similar to its antibacterial properties. For details of its pharmacokinetic properties and adverse effects, see Chapter 26.

Pyrantel and Oxantel Pamoate

Pyrantel pamoate is used to treat intestinal nematode infections, particularly hookworm and *Ascaris* infections, but is ineffective in trichuriasis. Conversely, its m-oxyphenol analogue, oxantel pamoate, exhibits trichuricidal activity[192] but lacks activity against hookworms and *Ascaris*.[6] For this reason, the drugs are often combined to provide broad coverage against intestinal helminths as part of mass treatment campaigns. A fixed combination dose, however, is no longer produced.

Both pyrantel and oxantel demonstrate a mechanism of action similar to levamisole—that is, by targeting the nicotinic acetylcholine receptor on the surface of nematode somatic muscle, thereby depolarizing the neuromuscular junction of the nematode resulting in irreversible paralysis and natural expulsion of the worm.[193] Although not clearly identified in humans, resistance is seen in parasites of domestic animals and is associated with modification of the nicotinic receptor.[194,195] Both pyrantel and oxantel pamoate are poorly soluble in water and thus are poorly absorbed from the intestine; more than 85% of the dose is passed unaltered in feces.[196] The absorbed portion of pyrantel is metabolized by the liver and excreted in urine; no human data exist for oxantel. Both agents are usually effective in a single dose. Safety in pregnancy and children younger than 2 years has not been established. It has minimal toxicity at doses used to treat intestinal helminth infection. Reported side effects are usually limited to anorexia, nausea, vomiting, abdominal cramps, and diarrhea.[197] Pyrantel has been shown to increase theophylline levels[198] and inhibit the anthelmintic activity of piperazine[199] and thus should not be given concomitantly. Oxantel enhances the activity of albendazole against *T. trichuria,* providing superior efficacy compared with albendazole alone.[6]

Levamisole

Levamisole is a rarely used anthelmintic agent. It is effective against *A. lumbricoides*[200] and *Ancylostoma duodenale*.[201] Similar to pyrantel, levamisole appears to act on nematode muscle, interfering with the function of a nicotinic acetylcholine receptor.[202] This depolarizes the muscle membrane and paralyzes the worm.[203] Resistance appears to be due to ion channel desensitization in the nicotinic acetylcholine receptor.[204] It is well absorbed orally and extensively metabolized in the liver.[205] Levamisole is excreted in the urine mainly as metabolites; only a small amount (<6%) is excreted in the feces.[206] The pharmacokinetics of levamisole have not been evaluated in patients with renal or hepatic disease, in children, or in elderly patients.[207] Animal studies with levamisole have not shown any evidence of teratogenicity. Nevertheless, treatment of pregnant women with levamisole should be deferred until after delivery. When used for the treatment of helminth infections, levamisole is well tolerated except for mild GI distress.[200]

Tribendimidine

Tribendimidine, a diamidine derivative of the aminophenylamidine amidantel, was developed at the National Institute of Parasitic Diseases in Shanghai, China, in the mid-1980s and represents the first new anthelmintic compound in 3 decades. It has a broad spectrum of activity against a wide variety of helminths including *Taenia* spp., intestinal nematodes (*A. lumbricoides*, hookworms, *T. trichiura*), and trematodes (*Opisthorchis viverrini* and *Clonorchis sinensis*).

Molecular studies on *Caenorhabditis elegans* suggest that tribendimidine is a cholinergic agonist that is selective for the nicotinic acetylcholine receptors of nematode muscle.[208] This action is similar to that of levamisole; however, tribendimidine has a much broader spectrum of activity.

Tribendimidine is converted to the active metabolite p-(1-dimethylamino ethylimino)aniline, known more simply as deacetylated amidantel (dADT). In healthy Chinese volunteers, dADT was detectable in plasma; while the parent drug was undetectable.[209] Evaluation of pharmacokinetic properties of tribendimidine in patients infected with *O. viverrini* demonstrated a variable t_{max} between 2–24 hours. Furthermore, AUC measurements of dADT over 24 hours demonstrated substantial differences in acetylation rates. Not surprisingly, patients cured of their infections showed significantly higher dADT serum concentrations and AUC values.[210,211] Food does not appear to affect the pharmacokinetics of tribendimidine when administered in the form of an enteric-coated tablet.[212] Clinical trials demonstrate efficacy of a single dose of tribendimidine alone[213] or in combination with other anthelmintics[214] against hookworm and concomitant soil-transmitted helminth infections. The clinical potential of this drug is yet to be determined, but it offers much promise.

Praziquantel

Praziquantel is highly active against a broad spectrum of trematodes and cestodes, with the exception of *F. hepatica*. It is the major drug used for treatment of schistosomiasis, including for community control programs for this disease. The drug is rapidly and reversibly taken up by flukes and tapeworms but not metabolized. It is a component of dual therapy with albendazole for neurocysticercosis and hydatid disease, as further discussed in Chapter 289.

The mechanism of action of praziquantel is incompletely understood, but evidence from animal models[215] and study of the drug's relative efficacy in schistosomiasis-naïve and endemic human populations[216] indicates that a preformed antiparasitic antibody response is required for optimal activity. Praziquantel disrupts the parasite tegument, causing tetanic contractures with loss of adherence to host tissues and, ultimately, disintegration or expulsion. It also interferes with parasite metabolism, exposing concealed antigens in the parasite.[217]

Reports from Senegal[218] and Egypt[219] of *Schistosoma mansoni* infection resistant to praziquantel and animal models have documented decreased efficacy.[220] The mechanisms of resistance remain unclear, but resistant strains were less susceptible to praziquantel-induced tegumental damage in vivo.[221] An investigation of the role of efflux pumps in this resistance suggested that modulation of Pgp with verapamil reversed resistance in vitro.[222] There have been no plausible reports of resistance in *Schistosoma haematobium* or *Schistosoma japonicum;* oxamniquine would be a treatment option for treatment of praziquantel-resistant *S. mansoni* infection. Praziquantel has been shown to have good activity against *Schistosoma mekongi* and *O. viverrini*.[223]

Praziquantel is rapidly absorbed with an estimated bioavailability of 80% to 100% but undergoes extensive first-pass hepatic metabolism to inactive metabolites so that most of the active drug does not reach the systemic circulation.[224] Praziquantel is completely metabolized, with 80% of the dose recovered as metabolites in urine within 4 days. It is not known to what extent praziquantel crosses the placenta, but only a small amount (<0.001%) is excreted in breast milk.[225] The bioavailability of praziquantel is influenced by other drugs. Phenytoin and carbamazepine both substantially reduce praziquantel levels by induction of first-pass hepatic metabolism and displacement of praziquantel from plasma protein binding.[226] Dexamethasone administered 24 hours earlier reduces the bioavailability of praziquantel by approximately 50%.[227] Praziquantel plasma levels are reduced by chloroquine and glucose. Levels of the drug are increased when it is taken with cimetidine and with food, particularly high-fat, high-carbohydrate meals.

Praziquantel is considered safe in children older than 2 years. Tablets can be divided but should not be chewed. It should be given with food and plenty of water because of its bitter taste. No dose adjustment is required in renal failure.[228] Praziquantel concentrations and side effects increase in proportion to the degree of hepatic impairment[229]; thus dose reduction may be indicated in these patients. In a rodent study, fetal death ensued when the drug was administered in high doses to pregnant rats between the 6th and 10th day of gestation.[230] Although there have been no reports of adverse maternal and fetal outcomes in large-scale treatment programs where inadvertent administration to women in early pregnancy was likely, it is recommended that praziquantel be withheld during the first trimester. It is also recommended that mothers should not breastfeed for 3 days after drug ingestion. A randomized, double-blind, placebo-controlled trial in 370 pregnant women in the

Philippines reported no significant differences with respect to the key indices of abortion, fetal death in utero, and congenital anomalies.[231] The integration of these new data into existing recommendations is awaited.

Praziquantel is well tolerated. The most commonly reported side effects are relatively mild and include transient nausea, vomiting, abdominal pain, dizziness, headache, and lassitude. Symptoms begin 30 minutes after ingestion, may require spasmolytics for relief, and usually disappear spontaneously after a few hours. In general, the adverse effects are related to the intensity and location of the infection, suggesting that they are due to the host immune response to release of parasite antigen.[232] In one study in an African population heavily infected with *S. mansoni,* the frequency of GI symptoms of abdominal pain and bloody diarrhea exceeded 50%.[233] However, in a large retrospective study of patients infected with *S. japonicum,* less than 0.5% had significant side effects attributable to the drug.[234]

Oxamniquine

Oxamniquine is a hydroxylated metabolite of a 2-aminotetra-hydroquinoline with activity against S. *mansoni*. After the development of praziquantel, it has assumed a minor role because of its narrower spectrum of action and its more pronounced toxicity profile. In addition, drug efficacy shows regional variation.[235]

The primary mode of action of oxamniquine seems to be mediated by adenosine triphosphate–dependent generation of an intermediate that alkylates essential macromolecules including DNA. After 4 to 8 days of treatment with oxamniquine, adult schistosomes show tegmental alterations similar to that induced by praziquantel. These changes result in disorganization of the suckers with which the worms attach to blood vessels. The worms lose attachment and then shift from the mesenteric veins to the lungs and liver, where they are destroyed. Female worms may return to the mesenteric veins but are unable to produce eggs.

Oxamniquine is well absorbed after oral administration.[236] Peak plasma concentrations are achieved 1 to 4 hours after oral administration of a 10-mg/kg dose.[237,238] The elimination half-life of oxamniquine is 2 hours. Oxamniquine is administered orally as a single dose and is well absorbed. Food slows absorption and reduces bioavailability.[239] About 70% of an administered dose is excreted in urine as a mixture of pharmacologically inactive metabolites. No dose adjustment is necessary in renal or hepatic disease.[237] Oxamniquine is mildly embryocidal in mice and rabbits at doses an order of magnitude greater than those used in humans. It is suggested that breastfeeding be delayed for at least 4 hours after administration of oxamniquine.

The drug can turn urine bright orange-red. Side effects are uncommon and usually mild at the recommended doses. However, hallucinations and seizures have been rarely reported.[240–242] No data are available on interactions with other drugs, but the ability of oxamniquine to inhibit CYP2D6 may be of clinical importance.[243]

Metrifonate

First introduced as an insecticide, this organophosphate compound has selective activity only against *S. haematobium*. It was introduced as a drug for humans in the 1960s.[244–246] The standard dose regimen is 7.5 to 10 mg/kg given three times at 14-day intervals; the drug is 19% to 48% effective against this parasite,[247] with egg reduction rates of up to 90% 4 weeks after the final dose.[248] Use of metrifonate has dramatically declined with the recognition that praziquantel has superior clinical properties, particularly because it can be given as a single dose and is now relatively inexpensive.[249] Metrifonate has been withdrawn from the WHO Model List of Essential Medicines.[250]

Metrifonate is converted nonenzymatically in the body to the active form, dichlorvos (2,2-dichlorovinyl dimethyl phosphate), which irreversibly inhibits acetylcholinesterase. Dichlorvos is more active against schistosomal cholinesterase than against the human enzyme.

Metrifonate is well absorbed after oral administration; peak plasma concentrations for both metrifonate and dichlorvos are reached within 1 to 2 hours of a single oral dose. Whole-blood concentrations of the active metabolite dichlorvos are about 1% of the parent drug. Elimination of metrifonate depends on its conversion to dichlorvos, which occurs nonenzymatically. Although there are no data in humans, animal studies show that both metrifonate and dichlorvos are degraded largely by hydrolysis. Metrifonate and dichlorvos are predominantly eliminated in the urine as glucuronides.[251]

After a single oral dose, metrifonate produces a 95% decrease in plasma cholinesterase activity within 6 hours, with a fairly rapid return to normal. Erythrocyte cholinesterase levels return to normal more gradually, usually requiring about 2.5 months.[248] Patients should not be exposed to neuromuscular blocking agents or organophosphate insecticides for at least 48 hours after treatment.

No serious side effects have been seen with recommended doses,[251,252] but side effects resulting from cholinergic stimulation (fatigue, muscular weakness, tremor, sweating, salivation, fainting, abdominal colic, diarrhea, nausea, vomiting, and bronchospasm) have been reported. These are relatively rare and subside within a few hours. There is a strong relationship between the occurrence of side effects and plasma concentrations.[253] Metrifonate potentiates the effect of succinylcholine. Food may delay the rate of its absorption.[254]

Niclosamide

Niclosamide is highly effective against a wide variety of intestinal tapeworms but not against tissue cestodes, such as echinococcosis or cysticercosis. Praziquantel is the preferred agent for treatment of tapeworm infection in most settings. Niclosamide has the unique indication for treatment of intestinal *T. solium* infection when it is desired to treat only the intestinal form. The scolex and proximal segments of the tapeworms are killed on contact with niclosamide and may be digested in the gut. There is theoretical concern that autoinfection may result from release of viable ova as the tapeworm disintegrates within the intestinal lumen. As a precaution, a brisk purgative is recommended to be given 2 hours after the first dose given for *T. solium* infections. The drug acts by uncoupling oxidative phosphorylation.[255] In vitro, niclosamide rapidly paralyzes the cestode. Little is known about the pharmacokinetics of niclosamide. Only a small amount of the drug is absorbed from the GI tract.[255]

Use of the drug is limited by side effects, necessary duration of therapy, recommended use of purgatives, and restricted availability. Tablets are given on an empty stomach in the morning after a liquid meal: for *T. solium*, 2 g as a single dose, 500 mg in a child younger than 2 years, and 1 g in a child 2 to 6 years of age. All doses are to be taken as a single dose after a light breakfast. For *Taenia saginata* infection in an adult, 1 g is taken after breakfast, and 1 g is taken an hour later; in a child younger than 2 years, 250 mg is given after breakfast, and 250 mg is given an hour later; and in a child 2 to 6 years of age, 500 mg is given after breakfast, and 500 mg is given an hour later. For treatment of hymenolepiasis in an adult, the initial dose is 2 g on the first day, followed by 1 g daily for 6 days.

Adverse effects of niclosamide are mild and infrequent and may include GI disturbances, lightheadedness, malaise, and pruritus.[255] Alcohol may enhance the absorption of niclosamide, thereby increasing the risk of side effects, and therefore should be avoided when taking this drug. Niclosamide is safe for use in pregnancy.

Nitazoxanide

Discussed in detail in Chapter 42, nitazoxanide is approved by the FDA for the treatment of cryptosporidiosis and giardiasis. Its benzamide moiety resembles that of niclosamide, and it was initially developed as a veterinary anthelmintic agent. It demonstrated acceptable effectiveness (94% after a first course) as an alternative treatment to triclabendazole for fascioliasis in Mexico.[256]

Bithionol

Bithionol is a little-used chlorinated bisphenol with activity against trematodes including *F. hepatica*[257] and *Paragonimus* spp.[258] Praziquantel or triclabendazole is generally preferred. It competitively inhibits electron transfer resulting in impaired anaerobic energy metabolism and trematode death. Its parasite specificity is due to its unique target in the parasite respiratory chain.

Bithionol is readily absorbed from the GI tract and is widely distributed throughout the body. Peak blood concentrations are achieved

within 4 to 8 hours after oral administration. A high blood concentration seems to be maintained when bithionol is administered at intervals of 2 to 3 days.[259] Excretion has been reported to be mainly through the kidneys.

Limited supplies of bithionol are available from the Centers for Disease Control and Prevention Drug Service. Bithionol is given as an oral dose of 30 to 50 mg/kg on alternate days for 10 to 15 doses. Data on dose adjustments in special groups are limited, but one study indicated safety in patients with altered renal or liver function.[260]

Adverse effects of bithionol are usually mild and transient and include anorexia, nausea, abdominal cramps, diarrhea, and urticaria.[257,258,261] Data on drug interactions are limited.

Key References

The complete reference list is available online at Expert Consult.

1. Sheth UK. Mechanisms of anthelmintic action. *Prog Drug Res*. 1975;19:147–157.
3. Lacey E, Brady RL, Prichard RK, et al. Comparison of inhibition of polymerisation of mammalian tubulin and helminth ovicidal activity by benzimidazole carbamates. *Vet Parasitol*. 1987;23:105–119.
4. Diawara A, Drake LJ, Suswillo RR, et al. Assays to detect beta-tubulin codon 200 polymorphism in *Trichuris trichiura* and *Ascaris lumbricoides*. *PLoS Negl Trop Dis*. 2009;3:e397.
5. Schwab AE, Boakye DA, Kyelem D, et al. Detection of benzimidazole resistance-associated mutations in the filarial nematode *Wuchereria bancrofti* and evidence for selection by albendazole and ivermectin combination treatment. *Am J Trop Med Hyg*. 2005;73:234–238.
9. Jung H, Medina L, Garcia L, et al. Absorption studies of albendazole and some physicochemical properties of the drug and its metabolite albendazole sulphoxide. *J Pharm Pharmacol*. 1998;50:43–48.
10. Justel A, Alvarez AI, Alonso ML, et al. Influence of ethanol on gastric absorption and metabolism of albendazole and mebendazole. *Drug Alcohol Depend*. 1994;36:49–55.
11. Rawden HC, Kokwaro GO, Ward SA, et al. Relative contribution of cytochromes P-450 and flavin-containing monoxygenases to the metabolism of albendazole by human liver microsomes. *Br J Clin Pharmacol*. 2000;49:313–322.
12. Gottschall DW, Theodorides VJ, Wang R. The metabolism of benzimidazole anthelmintics. *Parasitol Today*. 1990;6:115–124.
13. Delatour P, Benoit E, Besse S, et al. Comparative enantioselectivity in the sulphoxidation of albendazole in man, dogs and rats. *Xenobiotica*. 1991;21:217–221.
14. Takayanagui OM, Bonato PS, Dreossi SA, et al. Enantioselective distribution of albendazole metabolites in cerebrospinal fluid of patients with neurocysticercosis. *Br J Clin Pharmacol*. 2002;54:125–130.
15. Paredes A, de Campos Lourenco T, Marzal M, et al. In vitro analysis of albendazole sulfoxide enantiomers shows that (+)-(r)-albendazole sulfoxide is the active enantiomer against *Taenia solium*. *Antimicrob Agents Chemother*. 2013;57:944–949.
16. Mirfazaelian A, Dadashzadeh S, Rouini MR. Effect of gender in the disposition of albendazole metabolites in humans. *Eur J Clin Pharmacol*. 2002;58:403–408.
17. Mares SS, Jung CH, Lopez AT, et al. Influence of a Mexican diet on the bioavailability of albendazole. *Basic Clin Pharmacol Toxicol*. 2005;97:122–124.
19. Lange H, Eggers R, Bircher J. Increased systemic availability of albendazole when taken with a fatty meal. *Eur J Clin Pharmacol*. 1988;34:315–317.
20. Jung H, Hurtado M, Sanchez M, et al. Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J Clin Pharmacol*. 1992;32:28–31.
21. Nagy J, Schipper HG, Koopmans RP, et al. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. *Am J Trop Med Hyg*. 2002;66:260–263.
22. Kim RB, Wandel C, Leake B, et al. Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. *Pharm Res*. 1999;16:408–414.
24. Morris DL, Gould SE. Serum and cyst concentrations of mebendazole and flubendazole in hydatid disease. *Br Med J (Clin Res Ed)*. 1982;285:175.
25. Jung H, Hurtado M, Sanchez M, et al. Plasma and CSF levels of albendazole and praziquantel in patients with neurocysticercosis. *Clin Neuropharmacol*. 1990;13:559–564.
26. Mbendi N, Mashako MM, Lukuni N, et al. Albendazole in the treatment of intestinal nematodes in children less than 2 years of age. *Medicine et Chirurgie Digestives*. 1988;17:213–215.
27. Cotting J, Zeugin T, Steiger U, et al. Albendazole kinetics in patients with echinococcosis: delayed absorption and impaired elimination in cholestasis. *Eur J Clin Pharmacol*. 1990;38:605–608.
29. Olds GR, King C, Hewlett J, et al. Double-blind placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths. *J Infect Dis*. 1999;179:996–1003.
30. Reuter S, Jensen B, Buttenschoen K, et al. Benzimidazoles in the treatment of alveolar echinococcosis: a comparative study and review of the literature. *J Antimicrob Chemother*. 2000;46:451–456.
32. Dayan AD. Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. *Acta Trop*. 2003;86:141–159.
34. Webb EL, Kyosiimire-Lugemwa J, Kizito D, et al. The effect of anthelmintic treatment during pregnancy on HIV plasma viral load: results from a randomized, double-blind, placebo-controlled trial in Uganda. *J Acquir Immune Defic Syndr*. 2012;60:307–313.
37. Schipper HG, Koopmans RP, Nagy J, et al. Effect of dose increase or cimetidine co-administration on albendazole bioavailability. *Am J Trop Med Hyg*. 2000;63:270–273.
38. Corti N, Heck A, Rentsch K, et al. Effect of ritonavir on the pharmacokinetics of the benzimidazoles albendazole and mebendazole: an interaction study in healthy volunteers. *Eur J Clin Pharmacol*. 2009;65:999–1006.
39. Jung H, Hurtado M, Medina MT, et al. Dexamethasone increases plasma levels of albendazole. *J Neurol*. 1990;237:279–280.
40. Dawson M, Braithwaite PA, Roberts MS, et al. The pharmacokinetics and bioavailability of a tracer dose of [3H]-mebendazole in man. *Br J Clin Pharmacol*. 1985;19:79–86.
41. Bekhti A, Pirotte J. Cimetidine increases serum mebendazole concentrations. Implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol*. 1987;24:390–392.
42. Albonico M, Ramsan M, Wright V, et al. Soil-transmitted nematode infections and mebendazole treatment in Mafia Island schoolchildren. *Ann Trop Med Parasitol*. 2002;96:717–726.
43. Montresor A, Awasthi S, Crompton DW. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. *Acta Trop*. 2003;86:223–232.
44. Munst GJ, Karlaganis G, Bircher J. Plasma concentrations of mebendazole during treatment of echinococcosis: preliminary results. *Eur J Clin Pharmacol*. 1980;17:375–378.
46. Teggi A, Lastilla MG, De Rosa F. Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother*. 1993;37:1679–1684.
47. Franchi C, Di Vico B, Teggi A. Long-term evaluation of patients with hydatidosis treated with benzimidazole carbamates. *Clin Infect Dis*. 1999;29:304–309.
48. Fernandez-Banares F, Gonzalez-Huix F, Xiol X, et al. Marrow aplasia during high dose mebendazole treatment. *Am J Trop Med Hyg*. 1986;35:350–351.
49. Cowden J, Hotez P. Mebendazole and albendazole treatment of geohelminth infections in children and pregnant women. *Pediatr Infect Dis J*. 2000;19:659–660.
51. Larocque R, Casapia M, Gotuzzo E, et al. A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Trop Med Int Health*. 2006;11:1485–1495.
52. Robinson MW, Hoey EM, Fairweather I, et al. Characterisation of a beta-tubulin gene from the liver fluke, *Fasciola hepatica*. *Int J Parasitol*. 2001;31:1264–1268.
53. Kwa MS, Veenstra JG, Roos MH. Molecular characterisation of beta-tubulin genes present in benzimidazole-resistant populations of *Haemonchus contortus*. *Mol Biochem Parasitol*. 1993;60:133–143.
54. Toner E, Brennan GP, McConvery F, et al. A transmission electron microscope study on the route of entry of triclabendazole into the liver fluke, *Fasciola hepatica*. *Parasitology*. 2010;137:855–870.
55. Stitt AW, Fairweather I, Mackender RO. The effect of triclabendazole ("Fasinex") on protein synthesis by the liver fluke, *Fasciola hepatica*. *Int J Parasitol*. 1995;25:421–429.
56. Overend DJ, Bowen FL. Resistance of *Fasciola hepatica* to triclabendazole. *Aust Vet J*. 1995;72:275–276.
57. Winkelhagen AJ, Mank T, de Vries PJ, et al. Apparent triclabendazole-resistant human *Fasciola hepatica* infection, the Netherlands. *Emerg Infect Dis*. 2012;18:1028–1029.
58. Devine C, Brennan GP, Lanusse CE, et al. Potentiation of triclabendazole action in vivo against a triclabendazole-resistant isolate of *Fasciola hepatica* following its co-administration with the metabolic inhibitor, ketoconazole. *Vet Parasitol*. 2012;184:37–47.
59. Devine C, Brennan GP, Lanusse CE, et al. Potentiation of triclabendazole sulphoxide-induced tegumental disruption by methimazole in a triclabendazole-resistant isolate of *Fasciola hepatica*. *Parasitol Res*. 2010;106:1351–1363.
60. Lipkowitz KB, McCracken RO. A molecular modeling approach to in vivo efficacy of triclabendazole. *J Parasitol*. 1991;77:998–1005.
61. Lecaillon JB, Godbillon J, Campestrini J, et al. Effect of food on the bioavailability of triclabendazole in patients with fascioliasis. *Br J Clin Pharmacol*. 1998;45:601–604.
64. el Karaksy H, Hassanein B, Okasha S, et al. Human fascioliasis in Egyptian children: successful treatment with triclabendazole. *J Trop Pediatr*. 1999;45:135–138.
65. Apt W, Aguilera X, Vega F, et al. Treatment of human chronic fascioliasis with triclabendazole: drug efficacy and serologic response. *Am J Trop Med Hyg*. 1995;52:532–535.
66. Boix N, Teixido E, Vila-Cejudo M, et al. Triclabendazole sulfoxide causes stage-dependent embryolethality in zebrafish and mouse in vitro. *PLoS ONE*. 2015;10:e0121308.
68. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol*. 2002;42:1122–1133.
69. Amsden GW, Gregory TB, Michalak CA, et al. Pharmacokinetics of azithromycin and the combination of ivermectin and albendazole when administered alone and concurrently in healthy volunteers. *Am J Trop Med Hyg*. 2007;76:1153–1157.
70. Gonzalez Canga A, Sahagun Prieto AM, Diez Liebana MJ, et al. The pharmacokinetics and interactions of ivermectin in humans—a mini-review. *AAPS J*. 2008;10:42–46.
71. Shu EN, Onwujekwe EO, Okonkwo PO. Do alcoholic beverages enhance availability of ivermectin? *Eur J Clin Pharmacol*. 2000;56:437–438.
72. Baraka OZ, Mahmoud BM, Marschke CK, et al. Ivermectin distribution in the plasma and tissues of patients infected with *Onchocerca volvulus*. *Eur J Clin Pharmacol*. 1996;50:407–410.
73. Elkassaby MH. Ivermectin uptake and distribution in the plasma and tissue of Sudanese and Mexican patients infected with *Onchocerca volvulus*. *Trop Med Parasitol*. 1991;42:79–81.
74. Okonkwo PO, Ogbuokiri JE, Ofoegbu E, et al. Protein binding and ivermectin estimations in patients with onchocerciasis. *Clin Pharmacol Ther*. 1993;53:426–430.
75. Edwards G, Dingsdale A, Helsby N, et al. The relative systemic availability of ivermectin after administration as capsule, tablet, and oral solution. *Eur J Clin Pharmacol*. 1988;35:681–684.
76. Klotz U, Ogbuokiri JE, Okonkwo PO. Ivermectin binds avidly to plasma proteins. *Eur J Clin Pharmacol*. 1990;39:607–608.
77. Njoo FL, Beek WM, Keukens HJ, et al. Ivermectin detection in serum of onchocerciasis patients: relationship to adverse reactions. *Am J Trop Med Hyg*. 1995;52:94–97.
78. Krishna DR, Klotz U. Determination of ivermectin in human plasma by high-performance liquid chromatography. *Arzneimittelforschung*. 1993;43:609–611.
79. Cerkvenik Flajs V, Grabnar I. Ivermectin pharmacokinetics. *Slovenian Veterinary Research*. 2002;39.
80. Zeng Z, Andrew NW, Arison BH, et al. Identification of cytochrome P4503A4 as the major enzyme responsible for the metabolism of ivermectin by human liver microsomes. *Xenobiotica*. 1998;28:313–321.
81. Schinkel AH, Smit JJ, van Tellingen O, et al. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell*. 1994;77:491–502.

82. Molento MB, Lifschitz A, Sallovitz J, et al. Influence of verapamil on the pharmacokinetics of the antiparasitic drugs ivermectin and moxidectin in sheep. *Parasitol Res*. 2004;92:121–127.
83. Lespine A, Dupuy J, Orlowski S, et al. Interaction of ivermectin with multidrug resistance proteins (MRP1, 2 and 3). *Chem Biol Interact*. 2006;159:169–179.
84. Schrickx J, Fink-Gremmels J. D08 Ex vivo P-glycoprotein inhibition in porcine lymphocytes. *J Vet Pharmacol Ther*. 2006;29(s1):120.
85. Cross HF, Bronsvoort BM, Wahl G, et al. The entry of ivermectin and suramin into *Onchocerca ochengi* nodules. *Ann Trop Med Parasitol*. 1997;91:393–401.
86. Fink DW, Porras AG. Pharmacokinetics of ivermectin in animals and humans. In: Campbell W, ed. *Ivermectin and Abamectin*. New York: Springer-Verlag; 1989:113–130.
90. Mayer U, Wagenaar E, Dorobek B, et al. Full blockade of intestinal P-glycoprotein and extensive inhibition of blood-brain barrier P-glycoprotein by oral treatment of mice with PSC833. *J Clin Invest*. 1997;100:2430–2436.
91. Neff MW, Robertson KR, Wong AK, et al. Breed distribution and history of canine mdr1-1Delta, a pharmacogenetic mutation that marks the emergence of breeds from the collie lineage. *Proc Natl Acad Sci USA*. 2004;101:11725–11730.
92. Ito K, Uchida Y, Ohtsuki S, et al. Quantitative membrane protein expression at the blood-brain barrier of adult and younger cynomolgus monkeys. *J Pharm Sci*. 2011;100:3939–3950.
93. Chu X, Bleasby K, Evers R. Species differences in drug transporters and implications for translating preclinical findings to humans. *Expert Opin Drug Metab Toxicol*. 2013;9:237–252.
94. Eng JK, Blackhall WJ, Osei-Atweneboana MY, et al. Ivermectin selection on beta-tubulin: evidence in *Onchocerca volvulus* and *Haemonchus contortus*. *Mol Biochem Parasitol*. 2006;150:229–235.
95. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet*. 1997;349:1144–1145.
98. Duke BO, Zea-Flores G, Castro J, et al. Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *Am J Trop Med Hyg*. 1990;43:657–664.
99. Gardon J, Boussinesq M, Kamgno J, et al. Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomised controlled trial. *Lancet*. 2002;360:203–210.
102. Richards FO Jr, Eberhard ML, Bryan RT, et al. Comparison of high dose ivermectin and diethylcarbamazine for activity against bancroftian filariasis in Haiti. *Am J Trop Med Hyg*. 1991;44:3–10.
104. Kazura J, Greenberg J, Perry R, et al. Comparison of single-dose diethylcarbamazine and ivermectin for treatment of bancroftian filariasis in Papua New Guinea. *Am J Trop Med Hyg*. 1993;49:804–811.
105. Sunish IP, Rajendran R, Mani TR, et al. Impact of single dose of diethylcarbamazine and other antifilarial drug combinations on bancroftian filarial infection variables: assessment after 2 years. *Parasitol Int*. 2006;55:233–236.
106. Dreyer G, Addiss D, Noroes J, et al. Ultrasonographic assessment of the adulticidal efficacy of repeat high-dose ivermectin in bancroftian filariasis. *Trop Med Int Health*. 1996;1:427–432.
108. Yuvaraj J, Pani SP, Vanamail P, et al. Impact of seven rounds of mass administration of diethylcarbamazine and ivermectin on prevalence of chronic lymphatic filariasis in south India. *Trop Med Int Health*. 2008;13:737–742.
110. Shenoy RK, Kumaraswami V, Rajan K, et al. Ivermectin for the treatment of periodic malayan filariasis: a study of efficacy and side effects following a single oral dose and retreatment at six months. *Ann Trop Med Parasitol*. 1992;86:271–278.
111. Shenoy RK, Dalia S, John A, et al. Treatment of the microfilaraemia of asymptomatic brugian filariasis with single doses of ivermectin, diethylcarbamazine or albendazole, in various combinations. *Ann Trop Med Parasitol*. 1999;93:643–651.
112. Carme B, Ebikili B, Mbitsi A, et al. Therapeutic trial with ivermectin in loiasis with medium and high microfilaremia. *Ann Soc Belg Med Trop*. 1991;71:47–50.
113. Richard-Lenoble D, Kombila M, Rupp EA, et al. Ivermectin in loiasis and concomitant *O. volvulus* and *M. perstans* infections. *Am J Trop Med Hyg*. 1988;39:480–483.
114. Fischer P, Tukesiga E, Buttner DW. Long-term suppression of *Mansonella streptocerca* microfilariae after treatment with ivermectin. *J Infect Dis*. 1999;180:1403–1405.
115. Gonzalez AA, Chadee DD, Rawlins SC. Ivermectin treatment of mansonellosis in Trinidad. *West Indian Med J*. 1999;48:231–234.
116. Nutman TB, Nash TE, Ottesen EA. Ivermectin in the successful treatment of a patient with *Mansonella ozzardi* infection. *J Infect Dis*. 1987;156:662–665.
119. Datry A, Hilmarsdottir I, Mayorga-Sagastume R, et al. Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg*. 1994;88:344–345.
120. Shikiya K, Zaha O, Niimura S, et al. Clinical study on ivermectin against 125 strongyloidiasis patients. *Kansenshogaku Zasshi*. 1994;68:13–20.
121. Satoh M, Toma H, Sato Y, et al. Reduced efficacy of treatment of strongyloidiasis in HTLV-I carriers related to enhanced expression of IFN-gamma and TGF-beta1. *Clin Exp Immunol*. 2002;127:354–359.
124. Tarr PE, Miele PS, Peregoy KS, et al. Case report: rectal administration of ivermectin to a patient with *Strongyloides* hyperinfection syndrome. *Am J Trop Med Hyg*. 2003;68:453–455.
125. Bogoch II, Khan K, Abrams H, et al. Failure of ivermectin per rectum to achieve clinically meaningful serum levels in two cases of *Strongyloides* hyperinfection. *Am J Trop Med Hyg*. 2015;93:94–96.
126. Fusco DN, Downs JA, Satlin MJ, et al. Non-oral treatment with ivermectin for disseminated strongyloidiasis. *Am J Trop Med Hyg*. 2010;83:879–883.
127. Caumes E, Carriere J, Datry A, et al. A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg*. 1993;49:641–644.
128. Nontasut P, Claesson BA, Dekumyoy P, et al. Double-dose ivermectin vs albendazole for the treatment of gnathostomiasis. *Southeast Asian J Trop Med Public Health*. 2005;36:650–652.
129. Nontasut P, Bussaratid V, Chullawichit S, et al. Comparison of ivermectin and albendazole treatment for gnathostomiasis. *Southeast Asian J Trop Med Public Health*. 2000;31:374–377.
130. Bussaratid V, Krudsood S, Silachamroon U, et al. Tolerability of ivermectin in gnathostomiasis. *Southeast Asian J Trop Med Public Health*. 2005;36:644–649.
131. Wen LY, Yan XL, Sun FH, et al. A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. *Acta Trop*. 2008;106:190–194.
132. Freedman DO, Zierdt WS, Lujan A, et al. The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis*. 1989;159:1151–1153.
133. Naquira C, Jimenez G, Guerra JG, et al. Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg*. 1989;40:304–309.
134. Belizario VY, Amarillo ME, de Leon WU, et al. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. *Bull World Health Organ*. 2003;81:35–42.
135. Ismail MM, Jayakody RL. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of *Trichuris trichiura* infections in Sri Lanka. *Ann Trop Med Parasitol*. 1999;93:501–504.
136. Beach MJ, Streit TG, Addiss DG, et al. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *Am J Trop Med Hyg*. 1999;60:479–486.
141. Yoon KS, Strycharz JP, Baek JH, et al. Brief exposures of human body lice to sublethal amounts of ivermectin over-transcribes detoxification genes involved in tolerance. *Insect Mol Biol*. 2011;20:687–699.
142. Edwards G. Ivermectin: does P-glycoprotein play a role in neurotoxicity? *Filaria J*. 2003;2(suppl 1):S8.
143. Peters W, Robinson BL, Milhous WK. The chemotherapy of rodent malaria. LI. Studies on a new 8-aminoquinoline, WR 238,605. *Ann Trop Med Parasitol*. 1993;87:547–552.
144. Veit O, Beck B, Steuerwald M, et al. First case of ivermectin-induced severe hepatitis. *Trans R Soc Trop Med Hyg*. 2006;100:795–797.
145. Doumbo O, Soula G, Kodio B, et al. Ivermectin and pregnancy in mass treatment in Mali. *Bull Soc Pathol Exot*. 1992;85:247–251.
148. Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health*. 2003;8:1093–1101.
149. Ogbuokiri JE, Ozumba BC, Okonkwo PO. Ivermectin levels in human breastmilk. *Eur J Clin Pharmacol*. 1993;45:389–390.
150. Sangster N. Pharmacology of anthelmintic resistance. *Parasitology*. 1996;113(suppl):S201–S216.
152. APOC WHO. The World Health Organization Year 2010 Progress Report. 2010 (1st September 2009–31st August 2010).
153. Katabarwa MN, Eyamba A, Nwane P, et al. Seventeen years of annual distribution of ivermectin has not interrupted onchocerciasis transmission in North Region, Cameroon. *Am J Trop Med Hyg*. 2011;85:1041–1049.
154. Ali MM, Mukhtar MM, Baraka OZ, et al. Immunocompetence may be important in the effectiveness of Mectizan (ivermectin) in the treatment of human onchocerciasis. *Acta Trop*. 2002;84:49–53.
156. Awadzi K, Attah SK, Addy ET, et al. Thirty-month follow-up of sub-optimal responders to multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. *Ann Trop Med Parasitol*. 2004;98:359–370.
158. Bourguinat C, Pion SD, Kamgno J, et al. Genetic selection of low fertile *Onchocerca volvulus* by ivermectin treatment. *PLoS Negl Trop Dis*. 2007;1:e72.
159. Prichard R, Menez C, Lespine A. Moxidectin and the avermectins: consanguinity but not identity. *Int J Parasitol Drugs Drug Resist*. 2012;2:134–153.
160. James CE, Davey MW. Increased expression of ABC transport proteins is associated with ivermectin resistance in the model nematode *Caenorhabditis elegans*. *Int J Parasitol*. 2009;39:213–220.
161. Ardelli BF, Stitt LE, Tompkins JB, et al. A comparison of the effects of ivermectin and moxidectin on the nematode *Caenorhabditis elegans*. *Vet Parasitol*. 2009;165:96–108.
162. Bygarski EE, Prichard RK, Ardelli BF. Resistance to the macrocyclic lactone moxidectin is mediated in part by membrane transporter P-glycoproteins: implications for control of drug resistant parasitic nematodes. *Int J Parasitol Drugs Drug Resist*. 2014;4:143–151.
163. Janko C, Geyer J. Moxidectin has a lower neurotoxic potential but comparable brain penetration in P-glycoprotein-deficient CF-1 mice compared to ivermectin. *J Vet Pharmacol Ther*. 2013;36:275–284.
164. Menez C, Sutra JF, Prichard R, et al. Relative neurotoxicity of ivermectin and moxidectin in Mdr1ab (-/-) mice and effects on mammalian GABA(A) channel activity. *PLoS Negl Trop Dis*. 2012;6:e1883.
165. Godoy P, Che H, Beech RN, et al. Characterization of *Haemonchus contortus* P-glycoprotein-16 and its interaction with the macrocyclic lactone anthelmintics. *Mol Biochem Parasitol*. 2015;204:11–15.
166. Korth-Bradley JM, Parks V, Chalon S, et al. The effect of a high-fat breakfast on the pharmacokinetics of moxidectin in healthy male subjects: a randomized phase I trial. *Am J Trop Med Hyg*. 2012;86:122–125.
168. Awadzi K, Opoku NO, Attah SK, et al. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin in *Onchocerca volvulus* infection. *PLoS Negl Trop Dis*. 2014;8:e2953.
169. United States Food & Drug Administration. Drug Trials Snapshots: Moxidectin—Prescribing information 13 June 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf.
170. Korth-Bradley JM, Parks V, Chalon S, et al. Excretion of moxidectin into breast milk and pharmacokinetics in healthy lactating women. *Antimicrob Agents Chemother*. 2011;55:5200–5204.
171. Korth-Bradley JM, Parks V, Wagner F, et al. Effect of moxidectin on CYP3A4 activity as evaluated by oral midazolam pharmacokinetics in healthy subjects. *Clin Pharmacol Drug Dev*. 2013;3:151–157.
172. Cesbron JY, Capron A, Vargaftig BB, et al. Platelets mediate the action of diethylcarbamazine on microfilariae. *Nature*. 1987;325:533–536.
173. Liu LX, Weller PF. Intravascular filarial parasites inhibit platelet aggregation. Role of parasite-derived prostanoids. *J Clin Invest*. 1992;89:1113–1120.
174. Maizels RM, Denham DA. Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug. *Parasitology*. 1992;105(suppl):S49–S60.
175. Fujimaki Y, Ehara M, Kimura E, et al. Diethylcarbamazine, antifilarial drug, inhibits microtubule polymerization and disrupts preformed microtubules. *Biochem Pharmacol*. 1990;39:851–856.
176. Edwards G, Breckenridge AM, Adjepon-Yamoah KK, et al. The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol*. 1981;12:807–812.
177. Adjepon-Yamoah KK, Edwards G, Breckenridge AM, et al. The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol*. 1982;13:829–834.
178. Orme M, Edwards G, Awadzi K, et al. Clinical pharmacokinetics of drugs against onchocerciasis. *Acta Leiden*. 1990;59:329–342.
179. Joseph CA, Dixon PA. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol*. 1984;36:281–282.
180. Eberhard ML, Lammie PJ, Dickinson CM, et al. Evidence of nonsusceptibility to diethylcarbamazine in *Wuchereria bancrofti*. *J Infect Dis*. 1991;163:1157–1160.

181. Eberhard ML, Lowrie RC Jr, Lammie PJ. Persistence of microfilaremia in bancroftian filariasis after diethylcarbamazine citrate therapy. *Trop Med Parasitol*. 1988;39:128–130.
182. Noroes J, Dreyer G, Santos A, et al. Assessment of the efficacy of diethylcarbamazine on adult *Wuchereria bancrofti* in vivo. *Trans R Soc Trop Med Hyg*. 1997;91:78–81.
185. Bird AC, el Sheikh H, Anderson J, et al. Changes in visual function and in the posterior segment of the eye during treatment of onchocerciasis with diethylcarbamazine citrate. *Br J Ophthalmol*. 1980;64:191–200.
186. Dreyer G, Pires ML, de Andrade LD, et al. Tolerance of diethylcarbamazine by microfilaraemic and amicrofilaraemic individuals in an endemic area of bancroftian filariasis, Recife, Brazil. *Trans R Soc Trop Med Hyg*. 1994;88:232–236.
187. Carme B, Boulesteix J, Boutes H, et al. Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. *Am J Trop Med Hyg*. 1991;44: 684–690.
188. Taylor MJ, Bandi C, Hoerauf A. *Wolbachia* bacterial endosymbionts of filarial nematodes. *Adv Parasitol*. 2005;60:245–284.
191. Gayen P, Nayak A, Saini P, et al. A double-blind controlled field trial of doxycycline and albendazole in combination for the treatment of bancroftian filariasis in India. *Acta Trop*. 2013;125:150–156.
192. Keiser J, Tritten L, Silbereisen A, et al. Activity of oxantel pamoate monotherapy and combination chemotherapy against *Trichuris muris* and hookworms: revival of an old drug. *PLoS Negl Trop Dis*. 2013;7:e2119.
193. Aubry ML, Cowell P, Davey MJ, et al. Aspects of the pharmacology of a new anthelmintic: pyrantel. *Br J Pharmacol*. 1970;38:332–344.
194. Robertson AP, Bjorn HE, Martin RJ. Pyrantel resistance alters nematode nicotinic acetylcholine receptor single-channel properties. *Eur J Pharmacol*. 2000;394:1–8.
195. Kopp SR, Coleman GT, Traub RJ, et al. Acetylcholine receptor subunit genes from *Ancylostoma caninum*: altered transcription patterns associated with pyrantel resistance. *Int J Parasitol*. 2009;39:435–441.
196. Kimura Y, Kume M. Absorption, distribution, excretion and metabolism of pyrantel pamoate. *Pharmacometrics*. 1971;5:347–358.
197. Cervoni WA, Oliver-Gonzalez J. Clinical evaluation of pyrantel pamoate in helminthiasis. *Am J Trop Med Hyg*. 1971;20:589–591.
198. Loria P, Miller S, Foley M, et al. Inhibition of the peroxidative degradation of haem as the basis of action of chloroquine and other quinoline antimalarials. *Biochem J*. 1999;339(Pt 2):363–370.
199. Terada M, Fujiu Y, Sano M. Studies on chemotherapy of parasitic helminths (XVII). Effects of pyrantel on the motility of various parasitic helminths and isolated host tissues. *Experientia*. 1983;39:1020–1022.
200. Farid Z, Bassily S, Miner WF, et al. Comparative single/dose treatment of hookworm and roundworm infections with levamisole, pyrantel and bephenium. *J Trop Med Hyg*. 1977;80:107–108.
201. Holland CV, O'Shea E, Asaolu SO, et al. A cost-effectiveness analysis of anthelminthic intervention for community control of soil-transmitted helminth infection: levamisole and *Ascaris lumbricoides*. *J Parasitol*. 1996;82:527–530.
202. Martin RJ, Robertson AP, Bjorn H. Target sites of anthelmintics. *Parasitology*. 1997;114(suppl):S111–S124.
203. Atchison WD, Geary TG, Manning B, et al. Comparative neuromuscular blocking actions of levamisole and pyrantel-type anthelmintics on rat and gastrointestinal nematode somatic muscle. *Toxicol Appl Pharmacol*. 1992;112:133–143.
204. Robertson AP, Bjorn HE, Martin RJ. Resistance to levamisole resolved at the single-channel level. *FASEB J*. 1999;13:749–760.
205. Graziani G, de Martin GL. Pharmacokinetic studies on levamisole on the pharmacokinetics and relative bioavailability of levamisole in man. *Drugs Exp Clin Res*. 1977;2:235–240.
206. Adams JG. Pharmacokinetics of levamisole. *J Rheumatol Suppl*. 1978;4:137–142.
207. Edwards G, Breckenridge AM. Clinical pharmacokinetics of anthelmintic drugs. *Clin Pharmacokinet*. 1988;15:67–93.
209. Xiao SH, Utzinger J, Tanner M, et al. Advances with the Chinese anthelminthic drug tribendimidine in clinical trials and laboratory investigations. *Acta Trop*. 2013;126:115–126.
211. Vanobberghen F, Penny MA, Duthaler U, et al. Population pharmacokinetic modeling of tribendimidine metabolites in *Opisthorchis viverrini*-infected adults. *Antimicrob Agents Chemother*. 2016;60:5695–5704.
212. Yuan G, Zhang R, Wei C, et al. Effects of food on the pharmacokinetics of tribendimidine enteric-coated tablet in healthy Chinese subjects. *Lat Am J Pharm*. 2015;34:967–972.
215. Brindley PJ, Sher A. The chemotherapeutic effect of praziquantel against *Schistosoma mansoni* is dependent on host antibody response. *J Immunol*. 1987;139:215–220.
216. Gryseels B, Stelma FF, Talla I, et al. Epidemiology, immunology and chemotherapy of *Schistosoma mansoni* infections in a recently exposed community in Senegal. *Trop Geogr Med*. 1994;46(4 Spec No):209–219.
217. Xiao SH, Friedman PA, Catto BA, et al. Praziquantel-induced vesicle formation in the tegument of male *Schistosoma mansoni* is calcium dependent. *J Parasitol*. 1984;70:177–179.
218. Fallon PG, Sturrock RF, Niang AC, et al. Short report: diminished susceptibility to praziquantel in a Senegal isolate of *Schistosoma mansoni*. *Am J Trop Med Hyg*. 1995;53:61–62.
219. Ismail M, Metwally A, Farghaly A, et al. Characterization of isolates of *Schistosoma mansoni* from Egyptian villagers that tolerate high doses of praziquantel. *Am J Trop Med Hyg*. 1996;55:214–218.
220. Liang YS, Coles GC, Dai JR, et al. Biological characteristics of praziquantel-resistant and -susceptible isolates of *Schistosoma mansoni*. *Ann Trop Med Parasitol*. 2001;95:715–723.
221. William S, Botros S, Ismail M, et al. Praziquantel-induced tegumental damage in vitro is diminished in schistosomes derived from praziquantel-resistant infections. *Parasitology*. 2001;122(Pt 1):63–66.
222. Pinto-Almeida A, Mendes T, Armada A, et al. The role of efflux pumps in *Schistosoma mansoni* praziquantel resistant phenotype. *PLoS ONE*. 2015;10:e0140147.
223. Lovis L, Mak TK, Phongluxa K, et al. Efficacy of praziquantel against *Schistosoma mekongi* and *Opisthorchis viverrini*: a randomized, single-blinded dose-comparison trial. *PLoS Negl Trop Dis*. 2012;6: e1726.
224. Patzschke K, Putter J, Wegner LA, et al. Serum concentrations and renal excretion in humans after oral administration of praziquantel—results of three determination methods. *Eur J Drug Metab Pharmacokinet*. 1979;4:149–156.
225. Putter J, Held F. Quantitative studies on the occurrence of praziquantel in milk and plasma of lactating women. *Eur J Drug Metab Pharmacokinet*. 1979;4:193–198.
226. Bittencourt PR, Gracia CM, Martins R, et al. Phenytoin and carbamazepine decreased oral bioavailability of praziquantel. *Neurology*. 1992;42(3 Pt 1):492–496.
227. Vazquez ML, Jung H, Sotelo J. Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. *Neurology*. 1987;37:1561–1562.
228. Pehrson PO, Bengtsson E, Diekmann HW, et al. Treatment with praziquantel in a patient with schistosomiasis and chronic renal failure. *Trans R Soc Trop Med Hyg*. 1983;77:687–688.
229. Watt G, White NJ, Padre L, et al. Praziquantel pharmacokinetics and side effects in *Schistosoma japonicum*-infected patients with liver disease. *J Infect Dis*. 1988;157:530–535.
230. Montero R, Ostrosky P. Genotoxic activity of praziquantel. *Mutat Res*. 1997;387:123–139.
231. Olveda RM, Acosta LP, Tallo V, et al. Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2016;16:199–208.
232. Matsumoto J. Adverse effects of praziquantel treatment of *Schistosoma japonicum* infection: involvement of host anaphylactic reactions induced by parasite antigen release. *Int J Parasitol*. 2002;32:461–471.
233. Polderman AM, Gryseels B, Gerold JL, et al. Side effects of praziquantel in the treatment of *Schistosoma mansoni* in Maniema, Zaire. *Trans R Soc Trop Med Hyg*. 1984;78:752–754.
234. Chen MG, Fu S, Hua XJ, et al. A retrospective survey on side effects of praziquantel among 25,693 cases of schistosomiasis japonica. *Southeast Asian J Trop Med Public Health*. 1983;14:495–500.
235. Nash TE, Cheever AW, Ottesen EA, et al. Schistosome infections in humans: perspectives and recent findings. NIH conference. *Ann Intern Med*. 1982;97:740–754.
236. Kaye B, Woolhouse NM. The metabolism of oxamniquine—a new schistosomicide. *Ann Trop Med Parasitol*. 1976;70:323–328.
237. Daneshmend TK, Homeida MA. Oxamniquine pharmacokinetics in hepatosplenic schistosomiasis in the Sudan. *J Antimicrob Chemother*. 1987;19:87–93.
238. Kokwaro GO, Taylor G. Oxamniquine pharmacokinetics in healthy Kenyan African volunteers. *East Afr Med J*. 1991;68:359–364.
240. Al-Aska AK. Treatment of *Schistosoma mansoni* infection with oxamniquine in Riyadh, Saudi Arabia. *Trop Med Parasitol*. 1985;36:213–214.
241. Krajden S, Keystone JS, Glenn C. Safety and toxicity of oxamniquine in the treatment of *Schistosoma mansoni* infections, with particular reference to electroencephalographic abnormalities. *Am J Trop Med Hyg*. 1983;32:1344–1346.
242. Stokvis H, Bauer AG, Stuiver PC, et al. Seizures associated with oxamniquine therapy. *Am J Trop Med Hyg*. 1986;35:330–331.
243. Masimirembwa CM, Hasler JA, Johansson I. Inhibitory effects of antiparasitic drugs on cytochrome P450 2D6. *Eur J Clin Pharmacol*. 1995;48:35–38.
244. Forsyth DM, Rashid C. Treatment of urinary schistosomiasis. Practice and theory. *Lancet*. 1967;1:130–133.
245. Feldmeier H, Doehring E. Clinical experience with metrifonate. Review with emphasis on its use in endemic areas. *Acta Trop*. 1987;44:357–368.
246. Snellen WM. Therapeutic properties of metrifonate. *Acta Pharmacol Toxicol (Copenh)*. 1981;49(suppl 5):114–117.
248. Davis RP, Bailey DR. Effect of metrifonate on blood cholinesterases in children during the treatment of schistosomiasis. *Bull World Health Organ*. 1972;46: 747–759.
249. Feldmeier H, Chitsulo L. Therapeutic and operational profiles of metrifonate and praziquantel in *Schistosoma haematobium* infection. *Arzneimittelforschung*. 1999;49:557–565.
250. Cioli D. Praziquantel: is there real resistance and are there alternatives? *Curr Opin Infect Dis*. 2000;13: 659–663.
251. Holmstedt B, Nordgren I, Sandoz M, et al. Metrifonate. Summary of toxicological and pharmacological information available. *Arch Toxicol*. 1978;41:3–29.
252. Davis A, Bailey DR. Metrifonate in urinary schistosomiasis. *Bull World Health Organ*. 1969;41:209–224.
253. Aden-Abdi Y, Villen T, Ericsson O, et al. Metrifonate in healthy volunteers: interrelationship between pharmacokinetic properties, cholinesterase inhibition and side-effects. *Bull World Health Organ*. 1990;68:731–736.
254. Heinig R, Sachse R. The effect of food and time of administration on the pharmacokinetic and pharmacodynamic profile of metrifonate. *Int J Clin Pharmacol Ther*. 1999;37:456–464.
255. Pearson RD, Hewlett EL. Niclosamide therapy for tapeworm infections. *Ann Intern Med*. 1985;102: 550–551.
257. Bassiouny HK, Soliman NK, el Daly SM, et al. Human fascioliasis in Egypt: effect of infection and efficacy of bithionol treatment. *J Trop Med Hyg*. 1991;94:333–337.
258. Singh TS, Mutim SS, Razaque MA. Pulmonary paragonimiasis: clinical features, diagnosis, and treatment of 39 cases in Manipur. *Trans R Soc Trop Med Hyg*. 1986;80:967–971.
259. Yokogawa M, Iwasaki M, Shigeyasu M, et al. Chemotherapy of paragonimiasis with bithionol. V. Studies on the minimum effective dose and changes in abnormal x-ray shadows in the chest after treatment. *Am J Trop Med Hyg*. 1963;12:859–869.
260. Farag HF, Salem A, el Hifni SA, et al. Bithionol (Bitin) treatment in established fascioliasis in Egyptians. *J Trop Med Hyg*. 1988;91:240–244.
261. Bacq Y, Besnier JM, Duong TH, et al. Successful treatment of acute fascioliasis with bithionol. *Hepatology*. 1991;14:1066–1069.

References

1. Sheth UK. Mechanisms of anthelmintic action. *Prog Drug Res*. 1975;19:147–157.
2. Lacey E. Mode of action of benzimidazoles. *Parasitol Today*. 1990;6:112–115.
3. Lacey E, Brady RL, Prichard RK, et al. Comparison of inhibition of polymerisation of mammalian tubulin and helminth ovicidal activity by benzimidazole carbamates. *Vet Parasitol*. 1987;23:105–119.
4. Diawara A, Drake LJ, Suswillo RR, et al. Assays to detect beta-tubulin codon 200 polymorphism in *Trichuris trichiura* and *Ascaris lumbricoides*. *PLoS Negl Trop Dis*. 2009;3:e397.
5. Schwab AE, Boakye DA, Kyelem D, et al. Detection of benzimidazole resistance-associated mutations in the filarial nematode *Wuchereria bancrofti* and evidence for selection by albendazole and ivermectin combination treatment. *Am J Trop Med Hyg*. 2005;73:234–238.
6. Speich B, Ame SM, Ali SM, et al. Oxantel pamoate–albendazole for *Trichuris trichiura* infection. *N Engl J Med*. 2014;370:610–620.
7. Soukhathammavong PA, Sayasone S, Phongluxa K, et al. Low efficacy of single-dose albendazole and mebendazole against hookworm and effect on concomitant helminth infection in Lao PDR. *PLoS Negl Trop Dis*. 2012;6:e1417.
8. Horton RJ. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. *Acta Trop*. 1997;64:79–93.
9. Jung H, Medina L, Garcia L, et al. Absorption studies of albendazole and some physicochemical properties of the drug and its metabolite albendazole sulphoxide. *J Pharm Pharmacol*. 1998;50:43–48.
10. Justel A, Alvarez AI, Alonso ML, et al. Influence of ethanol on gastric absorption and metabolism of albendazole and mebendazole. *Drug Alcohol Depend*. 1994;36:49–55.
11. Rawden HC, Kokwaro GO, Ward SA, et al. Relative contribution of cytochromes P-450 and flavin-containing monoxygenases to the metabolism of albendazole by human liver microsomes. *Br J Clin Pharmacol*. 2000;49:313–322.
12. Gottschall DW, Theodorides VJ, Wang R. The metabolism of benzimidazole anthelmintics. *Parasitol Today*. 1990;6:115–124.
13. Delatour P, Benoit E, Besse S, et al. Comparative enantioselectivity in the sulphoxidation of albendazole in man, dogs and rats. *Xenobiotica*. 1991;21:217–221.
14. Takayanagui OM, Bonato PS, Dreossi SA, et al. Enantioselective distribution of albendazole metabolites in cerebrospinal fluid of patients with neurocysticercosis. *Br J Clin Pharmacol*. 2002;54:125–130.
15. Paredes A, de Campos Lourenco T, Marzal M, et al. In vitro analysis of albendazole sulfoxide enantiomers shows that (+)-(r)-albendazole sulfoxide is the active enantiomer against *Taenia solium*. *Antimicrob Agents Chemother*. 2013;57:944–949.
16. Mirfazaelian A, Dadashzadeh S, Rouini MR. Effect of gender in the disposition of albendazole metabolites in humans. *Eur J Clin Pharmacol*. 2002;58:403–408.
17. Mares SS, Jung CH, Lopez AT, et al. Influence of a Mexican diet on the bioavailability of albendazole. *Basic Clin Pharmacol Toxicol*. 2005;97:122–124.
18. Marriner SE, Morris DL, Dickson B, et al. Pharmacokinetics of albendazole in man. *Eur J Clin Pharmacol*. 1986;30:705–708.
19. Lange H, Eggers R, Bircher J. Increased systemic availability of albendazole when taken with a fatty meal. *Eur J Clin Pharmacol*. 1988;34:315–317.
20. Jung H, Hurtado M, Sanchez M, et al. Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J Clin Pharmacol*. 1992;32:28–31.
21. Nagy J, Schipper HG, Koopmans RP, et al. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. *Am J Trop Med Hyg*. 2002;66:260–263.
22. Kim RB, Wandel C, Leake B, et al. Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. *Pharm Res*. 1999;16:408–414.
23. Saimot AG, Meulemans A, Cremieux AC, et al. Albendazole as a potential treatment for human hydatidosis. *Lancet*. 1983;2:652–656.
24. Morris DL, Gould SE. Serum and cyst concentrations of mebendazole and flubendazole in hydatid disease. *Br Med J (Clin Res Ed)*. 1982;285:175.
25. Jung H, Hurtado M, Sanchez M, et al. Plasma and CSF levels of albendazole and praziquantel in patients with neurocysticercosis. *Clin Neuropharmacol*. 1990;13:559–564.
26. Mbendi N, Mashako MM, Lukuni N, et al. Albendazole in the treatment of intestinal nematodes in children less than 2 years of age. *Medicine et Chirurgie Digestives*. 1988;17:213–215.
27. Cotting J, Zeugin T, Steiger U, et al. Albendazole kinetics in patients with echinococcosis: delayed absorption and impaired elimination in cholestasis. *Eur J Clin Pharmacol*. 1990;38:605–608.
28. Horton J. Albendazole: a review of anthelmintic efficacy and safety in humans. *Parasitology*. 2000;121(suppl):S113–S132.
29. Olds GR, King C, Hewlett J, et al. Double-blind placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths. *J Infect Dis*. 1999;179:996–1003.
30. Reuter S, Jensen B, Buttenschoen K, et al. Benzimidazoles in the treatment of alveolar echinococcosis: a comparative study and review of the literature. *J Antimicrob Chemother*. 2000;46:451–456.
31. Stojkovic M, Zwahlen M, Teggi A, et al. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. *PLoS Negl Trop Dis*. 2009;3:e524.
32. Dayan AD. Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. *Acta Trop*. 2003;86:141–159.
33. Ndibazza J, Muhangi L, Akishule D, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: a randomized controlled trial. *Clin Infect Dis*. 2010;50:531–540.
34. Webb EL, Kyosiimire-Lugemwa J, Kizito D, et al. The effect of anthelmintic treatment during pregnancy on HIV plasma viral load: results from a randomized, double-blind, placebo-controlled trial in Uganda. *J Acquir Immune Defic Syndr*. 2012;60:307–313.
35. Webb EL, Mawa PA, Ndibazza J, et al. Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377:52–62.
36. Elliott AM, Ndibazza J, Mpairwe H, et al. Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child? *Parasitology*. 2011;138:1499–1507.
37. Schipper HG, Koopmans RP, Nagy J, et al. Effect of dose increase or cimetidine co-administration on albendazole bioavailability. *Am J Trop Med Hyg*. 2000;63:270–273.
38. Corti N, Heck A, Rentsch K, et al. Effect of ritonavir on the pharmacokinetics of the benzimidazoles albendazole and mebendazole: an interaction study in healthy volunteers. *Eur J Clin Pharmacol*. 2009;65:999–1006.
39. Jung H, Hurtado M, Medina MT, et al. Dexamethasone increases plasma levels of albendazole. *J Neurol*. 1990;237:279–280.
40. Dawson M, Braithwaite PA, Roberts MS, et al. The pharmacokinetics and bioavailability of a tracer dose of [3H]-mebendazole in man. *Br J Clin Pharmacol*. 1985;19:79–86.
41. Bekhti A, Pirotte J. Cimetidine increases serum mebendazole concentrations. Implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol*. 1987;24:390–392.
42. Albonico M, Ramsan M, Wright V, et al. Soil-transmitted nematode infections and mebendazole treatment in Mafia Island schoolchildren. *Ann Trop Med Parasitol*. 2002;96:717–726.
43. Montresor A, Awasthi S, Crompton DW. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. *Acta Trop*. 2003;86:223–232.
44. Munst GJ, Karlaganis G, Bircher J. Plasma concentrations of mebendazole during treatment of echinococcosis: preliminary results. *Eur J Clin Pharmacol*. 1980;17:375–378.
45. Knopp S, Mohammed KA, Speich B, et al. Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis*. 2010;51:1420–1428.
46. Teggi A, Lastilla MG, De Rosa F. Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother*. 1993;37:1679–1684.
47. Franchi C, Di Vico B, Teggi A. Long-term evaluation of patients with hydatidosis treated with benzimidazole carbamates. *Clin Infect Dis*. 1999;29:304–309.
48. Fernandez-Banares F, Gonzalez-Huix F, Xiol X, et al. Marrow aplasia during high dose mebendazole treatment. *Am J Trop Med Hyg*. 1986;35:350–351.
49. Cowden J, Hotez P. Mebendazole and albendazole treatment of geohelminth infections in children and pregnant women. *Pediatr Infect Dis J*. 2000;19:659–660.
50. de Silva NR, Sirisena JL, Gunasekera DP, et al. Effect of mebendazole therapy during pregnancy on birth outcome. *Lancet*. 1999;353:1145–1149.
51. Larocque R, Casapia M, Gotuzzo E, et al. A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Trop Med Int Health*. 2006;11:1485–1495.
52. Robinson MW, Hoey EM, Fairweather I, et al. Characterisation of a beta-tubulin gene from the liver fluke, *Fasciola hepatica*. *Int J Parasitol*. 2001;31:1264–1268.
53. Kwa MS, Veenstra JG, Roos MH. Molecular characterisation of beta-tubulin genes present in benzimidazole-resistant populations of *Haemonchus contortus*. *Mol Biochem Parasitol*. 1993;60:133–143.
54. Toner E, Brennan GP, McConvery F, et al. A transmission electron microscope study on the route of entry of triclabendazole into the liver fluke, *Fasciola hepatica*. *Parasitology*. 2010;137:855–870.
55. Stitt AW, Fairweather I, Mackender RO. The effect of triclabendazole ("Fasinex") on protein synthesis by the liver fluke, *Fasciola hepatica*. *Int J Parasitol*. 1995;25:421–429.
56. Overend DJ, Bowen FL. Resistance of *Fasciola hepatica* to triclabendazole. *Aust Vet J*. 1995;72:275–276.
57. Winkelhagen AJ, Mank T, de Vries PJ, et al. Apparent triclabendazole-resistant human *Fasciola hepatica* infection, the Netherlands. *Emerg Infect Dis*. 2012;18:1028–1029.
58. Devine C, Brennan GP, Lanusse CE, et al. Potentiation of triclabendazole action in vivo against a triclabendazole-resistant isolate of *Fasciola hepatica* following its co-administration with the metabolic inhibitor, ketoconazole. *Vet Parasitol*. 2012;184:37–47.
59. Devine C, Brennan GP, Lanusse CE, et al. Potentiation of triclabendazole sulphoxide-induced tegumental disruption by methimazole in a triclabendazole-resistant isolate of *Fasciola hepatica*. *Parasitol Res*. 2010;106:1351–1363.
60. Lipkowitz KB, McCracken RO. A molecular modeling approach to in vivo efficacy of triclabendazole. *J Parasitol*. 1991;77:998–1005.
61. Lecaillon JB, Godbillon J, Campestrini J, et al. Effect of food on the bioavailability of triclabendazole in patients with fascioliasis. *Br J Clin Pharmacol*. 1998;45:601–604.
62. Villegas F, Angles R, Barrientos R, et al. Administration of triclabendazole is safe and effective in controlling fascioliasis in an endemic community of the Bolivian Altiplano. *PLoS Negl Trop Dis*. 2012;6:e1720.
63. Calvopina M, Guderian RH, Paredes W, et al. Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg*. 1998;92:566–569.
64. el Karaksy H, Hassanein B, Okasha S, et al. Human fascioliasis in Egyptian children: successful treatment with triclabendazole. *J Trop Pediatr*. 1999;45:135–138.
65. Apt W, Aguilera X, Vega F, et al. Treatment of human chronic fascioliasis with triclabendazole: drug efficacy and serologic response. *Am J Trop Med Hyg*. 1995;52:532–535.
66. Boix N, Teixido E, Vila-Cejudo M, et al. Triclabendazole sulfoxide causes stage-dependent embryolethality in zebrafish and mouse in vitro. *PLoS ONE*. 2015;10:e0121308.
67. Campbell WC, Fisher MH, Stapley EO, et al. Ivermectin: a potent new antiparasitic agent. *Science*. 1983;221:823–828.
68. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol*. 2002;42:1122–1133.
69. Amsden GW, Gregory TB, Michalak CA, et al. Pharmacokinetics of azithromycin and the combination of ivermectin and albendazole when administered alone and concurrently in healthy volunteers. *Am J Trop Med Hyg*. 2007;76:1153–1157.
70. Gonzalez Canga A, Sahagun Prieto AM, Diez Liebana MJ, et al. The pharmacokinetics and interactions of ivermectin in humans—a mini-review. *AAPS J*. 2008;10:42–46.
71. Shu EN, Onwujekwe EO, Okonkwo PO. Do alcoholic beverages enhance availability of ivermectin? *Eur J Clin Pharmacol*. 2000;56:437–438.
72. Baraka OZ, Mahmoud BM, Marschke CK, et al. Ivermectin distribution in the plasma and tissues of patients infected with Onchocerca volvulus. *Eur J Clin Pharmacol*. 1996;50:407–410.
73. Elkassaby MH. Ivermectin uptake and distribution in the plasma and tissue of Sudanese and Mexican patients infected with Onchocerca volvulus. *Trop Med Parasitol*. 1991;42:79–81.
74. Okonkwo PO, Ogbuokiri JE, Ofoegbu E, et al. Protein binding and ivermectin estimations in patients with onchocerciasis. *Clin Pharmacol Ther*. 1993;53:426–430.
75. Edwards G, Dingsdale A, Helsby N, et al. The relative systemic availability of ivermectin after administration as capsule, tablet, and oral solution. *Eur J Clin Pharmacol*. 1988;35:681–684.

76. Klotz U, Ogbuokiri JE, Okonkwo PO. Ivermectin binds avidly to plasma proteins. *Eur J Clin Pharmacol*. 1990;39:607–608.
77. Njoo FL, Beek WM, Keukens HJ, et al. Ivermectin detection in serum of onchocerciasis patients: relationship to adverse reactions. *Am J Trop Med Hyg*. 1995;52:94–97.
78. Krishna DR, Klotz U. Determination of ivermectin in human plasma by high-performance liquid chromatography. *Arzneimittelforschung*. 1993;43:609–611.
79. Cerkvenik Flajs V, Grabnar I. Ivermectin pharmacokinetics. *Slovenian Vetinary Research*. 2002;39.
80. Zeng Z, Andrew NW, Arison BH, et al. Identification of cytochrome P4503A4 as the major enzyme responsible for the metabolism of ivermectin by human liver microsomes. *Xenobiotica*. 1998;28:313–321.
81. Schinkel AH, Smit JJ, van Tellingen O, et al. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell*. 1994;77:491–502.
82. Molento MB, Lifschitz A, Sallovitz J, et al. Influence of verapamil on the pharmacokinetics of the antiparasitic drugs ivermectin and moxidectin in sheep. *Parasitol Res*. 2004;92:121–127.
83. Lespine A, Dupuy J, Orlowski S, et al. Interaction of ivermectin with multidrug resistance proteins (MRP1, 2 and 3). *Chem Biol Interact*. 2006;159:169–179.
84. Schrickx J, Fink-Gremmels J. D08 Ex vivo P-glycoprotein inhibition in porcine lymphocytes. *J Vet Pharmacol Ther*. 2006;29(s1):120.
85. Cross HF, Bronsvoort BM, Wahl G, et al. The entry of ivermectin and suramin into *Onchocerca ochengi* nodules. *Ann Trop Med Parasitol*. 1997;91:393–401.
86. Fink DW, Porras AG. Pharmacokinetics of ivermectin in animals and humans. In: Campbell W, ed. *Ivermectin and Abamectin*. New York: Springer-Verlag; 1989:113–130.
87. Turner SA, Maclean JD, Fleckenstein L, et al. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. *Am J Trop Med Hyg*. 2005;73:911–914.
88. Zeitler K, Jariwala R, Restrepo-Jaramillo R, et al. Successful use of subcutaneous ivermectin for the treatment of *Strongyloides stercoralis* hyperinfection in the setting of small bowel obstruction and paralytic ileus in the immunocompromised population. *BMJ Case Rep*. 2018;2018.
89. Marty FM, Lowry CM, Rodriguez M, et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. *Clin Infect Dis*. 2005;41:e5–e8.
90. Mayer U, Wagenaar E, Dorobek B, et al. Full blockade of intestinal P-glycoprotein and extensive inhibition of blood-brain barrier P-glycoprotein by oral treatment of mice with PSC833. *J Clin Invest*. 1997;100:2430–2436.
91. Neff MW, Robertson KR, Wong AK, et al. Breed distribution and history of canine mdr1-1Delta, a pharmacogenetic mutation that marks the emergence of breeds from the collie lineage. *Proc Natl Acad Sci USA*. 2004;101:11725–11730.
92. Ito K, Uchida Y, Ohtsuki S, et al. Quantitative membrane protein expression at the blood-brain barrier of adult and younger cynomolgus monkeys. *J Pharm Sci*. 2011;100:3939–3950.
93. Chu X, Bleasby K, Evers R. Species differences in drug transporters and implications for translating preclinical findings to humans. *Expert Opin Drug Metab Toxicol*. 2013;9:237–252.
94. Eng JK, Blackhall WJ, Osei-Atweneboana MY, et al. Ivermectin selection on beta-tubulin: evidence in *Onchocerca volvulus* and *Haemonchus contortus*. *Mol Biochem Parasitol*. 2006;150:229–235.
95. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet*. 1997;349:1144–1145.
96. Basanez MG, Pion SD, Boakes E, et al. Effect of single-dose ivermectin on *Onchocerca volvulus*: a systematic review and meta-analysis. *Lancet Infect Dis*. 2008;8:310–322.
97. Goa KL, McTavish D, Clissold SP. Ivermectin. A review of its antifilarial activity, pharmacokinetic properties and clinical efficacy in onchocerciasis. *Drugs*. 1991;42:640–658.
98. Duke BO, Zea-Flores G, Castro J, et al. Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *Am J Trop Med Hyg*. 1990;43:657–664.
99. Gardon J, Boussinesq M, Kamgno J, et al. Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomised controlled trial. *Lancet*. 2002;360:203–210.
100. King CL, Suamani J, Sanuku N, et al. A trial of a triple-drug treatment for lymphatic filariasis. *N Engl J Med*. 2018;379:1801–1810.
101. Kumaraswami V, Ottesen EA, Vijayasekaran V, et al. Ivermectin for the treatment of *Wuchereria bancrofti* filariasis. Efficacy and adverse reactions. *JAMA*. 1988;259:3150–3153.
102. Richards FO Jr, Eberhard ML, Bryan RT, et al. Comparison of high dose ivermectin and diethylcarbamazine for activity against bancroftian filariasis in Haiti. *Am J Trop Med Hyg*. 1991;44:3–10.
103. Eberhard ML, Hightower AW, McNeeley DF, et al. Long-term suppression of microfilaraemia following ivermectin treatment. *Trans R Soc Trop Med Hyg*. 1992;86:287–288.
104. Kazura J, Greenberg J, Perry R, et al. Comparison of single-dose diethylcarbamazine and ivermectin for treatment of bancroftian filariasis in Papua New Guinea. *Am J Trop Med Hyg*. 1993;49:804–811.
105. Sunish IP, Rajendran R, Mani TR, et al. Impact of single dose of diethylcarbamazine and other antifilarial drug combinations on bancroftian filarial infection variables: assessment after 2 years. *Parasitol Int*. 2006;55:233–236.
106. Dreyer G, Addiss D, Noroes J, et al. Ultrasonographic assessment of the adulticidal efficacy of repeat high-dose ivermectin in bancroftian filariasis. *Trop Med Int Health*. 1996;1:427–432.
107. Ramaiah KD, Das PK, Vanamail P, et al. Impact of 10 years of diethylcarbamazine and ivermectin mass administration on infection and transmission of lymphatic filariasis. *Trans R Soc Trop Med Hyg*. 2007;101:555–563.
108. Yuvaraj J, Pani SP, Vanamail P, et al. Impact of seven rounds of mass administration of diethylcarbamazine and ivermectin on prevalence of chronic lymphatic filariasis in south India. *Trop Med Int Health*. 2008;13:737–742.
109. Thomsen EK, Sanuku N, Baea M, et al. Efficacy, safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and ivermectin for treatment of bancroftian filariasis. *Clin Infect Dis*. 2016;62:334–341.
110. Shenoy RK, Kumaraswami V, Rajan K, et al. Ivermectin for the treatment of periodic malayan filariasis: a study of efficacy and side effects following a single oral dose and retreatment at six months. *Ann Trop Med Parasitol*. 1992;86:271–278.
111. Shenoy RK, Dalia S, John A, et al. Treatment of the microfilaraemia of asymptomatic brugian filariasis with single doses of ivermectin, diethylcarbamazine or albendazole, in various combinations. *Ann Trop Med Parasitol*. 1999;93:643–651.
112. Carme B, Ebikili B, Mbitsi A, et al. Therapeutic trial with ivermectin in loiasis with medium and high microfilaremia. *Ann Soc Belg Med Trop*. 1991;71:47–50.
113. Richard-Lenoble D, Kombila M, Rupp EA, et al. Ivermectin in loiasis and concomitant *O. volvulus* and *M. perstans* infections. *Am J Trop Med Hyg*. 1988;39:480–483.
114. Fischer P, Tukesiga E, Buttner DW. Long-term suppression of *Mansonella streptocerca* microfilariae after treatment with ivermectin. *J Infect Dis*. 1999;180:1403–1405.
115. Gonzalez AA, Chadee DD, Rawlins SC. Ivermectin treatment of mansonellosis in Trinidad. *West Indian Med J*. 1999;48:231–234.
116. Nutman TB, Nash TE, Ottesen EA. Ivermectin in the successful treatment of a patient with Mansonella ozzardi infection. *J Infect Dis*. 1987;156:662–665.
117. Marti H, Haji HJ, Savioli L, et al. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg*. 1996;55:477–481.
118. Gann PH, Neva FA, Gam AA. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis*. 1994;169:1076–1079.
119. Datry A, Hilmarsdottir I, Mayorga-Sagastume R, et al. Treatment of *Strongyloides stercoralis* infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg*. 1994;88:344–345.
120. Shikiya K, Zaha O, Niimura S, et al. Clinical study on ivermectin against 125 strongyloidiasis patients. *Kansenshogaku Zasshi*. 1994;68:13–20.
121. Satoh M, Toma H, Sato Y, et al. Reduced efficacy of treatment of strongyloidiasis in HTLV-I carriers related to enhanced expression of IFN-gamma and TGF-beta1. *Clin Exp Immunol*. 2002;127:354–359.
122. Pacanowski J, Santos MD, Roux A, et al. Subcutaneous ivermectin as a safe salvage therapy in *Strongyloides stercoralis* hyperinfection syndrome: a case report. *Am J Trop Med Hyg*. 2005;73:122–124.
123. Barrett J, Broderick C, Soulsby H, et al. Subcutaneous ivermectin use in the treatment of severe *Strongyloides stercoralis* infection: two case reports and a discussion of the literature. *J Antimicrob Chemother*. 2016;71:220–225.
124. Tarr PE, Miele PS, Peregoy KS, et al. Case report: rectal administration of ivermectin to a patient with *Strongyloides* hyperinfection syndrome. *Am J Trop Med Hyg*. 2003;68:453–455.
125. Bogoch II, Khan K, Abrams H, et al. Failure of ivermectin per rectum to achieve clinically meaningful serum levels in two cases of Strongyloides hyperinfection. *Am J Trop Med Hyg*. 2015;93:94–96.
126. Fusco DN, Downs JA, Satlin MJ, et al. Non-oral treatment with ivermectin for disseminated strongyloidiasis. *Am J Trop Med Hyg*. 2010;83:879–883.
127. Caumes E, Carriere J, Datry A, et al. A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg*. 1993;49:641–644.
128. Nontasut P, Claesson BA, Dekumyoy P, et al. Double-dose ivermectin vs albendazole for the treatment of gnathostomiasis. *Southeast Asian J Trop Med Public Health*. 2005;36:650–652.
129. Nontasut P, Bussaratid V, Chullawichit S, et al. Comparison of ivermectin and albendazole treatment for gnathostomiasis. *Southeast Asian J Trop Med Public Health*. 2000;31:374–377.
130. Bussaratid V, Krudsood S, Silachamroon U, et al. Tolerability of ivermectin in gnathostomiasis. *Southeast Asian J Trop Med Public Health*. 2005;36:644–649.
131. Wen LY, Yan XL, Sun FH, et al. A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. *Acta Trop*. 2008;106:190–194.
132. Freedman DO, Zierdt WS, Lujan A, et al. The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis*. 1989;159:1151–1153.
133. Naquira C, Jimenez G, Guerra JG, et al. Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg*. 1989;40:304–309.
134. Belizario VY, Amarillo ME, de Leon WU, et al. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against Ascaris and Trichuris spp. *Bull World Health Organ*. 2003;81:35–42.
135. Ismail MM, Jayakody RL. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of *Trichuris trichiura* infections in Sri Lanka. *Ann Trop Med Parasitol*. 1999;93:501–504.
136. Beach MJ, Streit TG, Addiss DG, et al. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *Am J Trop Med Hyg*. 1999;60:479–486.
137. Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. *N Engl J Med*. 2010;362:717–725.
138. Foucault C, Ranque S, Badiaga S, et al. Oral ivermectin in the treatment of body lice. *J Infect Dis*. 2006;193:474–476.
139. DelGiudice P, Carles M, Couppie P, et al. Successful treatment of crusted (Norwegian) scabies with ivermectin in two patients with human immunodeficiency virus infection. *Br J Dermatol*. 1996;135:494–495.
140. Pariser DM, Meinking TL, Bell M, et al. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med*. 2012;367:1687–1693.
141. Yoon KS, Strycharz JP, Baek JH, et al. Brief exposures of human body lice to sublethal amounts of ivermectin over-transcribes detoxification genes involved in tolerance. *Insect Mol Biol*. 2011;20:687–699.
142. Edwards G. Ivermectin: does P-glycoprotein play a role in neurotoxicity? *Filaria J*. 2003;2(suppl 1):S8.
143. Peters W, Robinson BL, Milhous WK. The chemotherapy of rodent malaria. LI. Studies on a new 8-aminoquinoline, WR 238,605. *Ann Trop Med Parasitol*. 1993;87:547–552.
144. Veit O, Beck B, Steuerwald M, et al. First case of ivermectin-induced severe hepatitis. *Trans R Soc Trop Med Hyg*. 2006;100:795–797.
145. Doumbo O, Soula G, Kodio B, et al. Ivermectin and pregnancy in mass treatment in Mali. *Bull Soc Pathol Exot*. 1992;85:247–251.
146. Chippaux JP, Gardon-Wendel N, Gardon J, et al. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg*. 1993;87:318.
147. Pacque M, Munoz B, Poetschke G, et al. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet*. 1990;336:1486–1489.
148. Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health*. 2003;8:1093–1101.
149. Ogbuokiri JE, Ozumba BC, Okonkwo PO. Ivermectin levels in human breastmilk. *Eur J Clin Pharmacol*. 1993;45:389–390.

150. Sangster N. Pharmacology of anthelmintic resistance. *Parasitology*. 1996;113(suppl):S201–S216.
151. Basanez MG, Pion SD, Churcher TS, et al. River blindness: a success story under threat? *PLoS Med*. 2006;3:e371.
152. APOC WHO. The World Health Organization Year 2010 Progress Report. 2010 (1st September 2009–31st August 2010).
153. Katabarwa MN, Eyamba A, Nwane P, et al. Seventeen years of annual distribution of ivermectin has not interrupted onchocerciasis transmission in North Region, Cameroon. *Am J Trop Med Hyg*. 2011;85:1041–1049.
154. Ali MM, Mukhtar MM, Baraka OZ, et al. Immunocompetence may be important in the effectiveness of Mectizan (ivermectin) in the treatment of human onchocerciasis. *Acta Trop*. 2002;84:49–53.
155. Awadzi K, Boakye DA, Edwards G, et al. An investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. *Ann Trop Med Parasitol*. 2004;98:231–249.
156. Awadzi K, Attah SK, Addy ET, et al. Thirty-month follow-up of sub-optimal responders to multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. *Ann Trop Med Parasitol*. 2004;98:359–370.
157. Osei-Atweneboana MY, Eng JK, Boakye DA, et al. Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. *Lancet*. 2007;369:2021–2029.
158. Bourguinat C, Pion SD, Kamgno J, et al. Genetic selection of low fertile *Onchocerca volvulus* by ivermectin treatment. *PLoS Negl Trop Dis*. 2007;1:e72.
159. Prichard R, Menez C, Lespine A. Moxidectin and the avermectins: consanguinity but not identity. *Int J Parasitol Drugs Drug Resist*. 2012;2:134–153.
160. James CE, Davey MW. Increased expression of ABC transport proteins is associated with ivermectin resistance in the model nematode *Caenorhabditis elegans*. *Int J Parasitol*. 2009;39:213–220.
161. Ardelli BF, Stitt LE, Tompkins JB, et al. A comparison of the effects of ivermectin and moxidectin on the nematode *Caenorhabditis elegans*. *Vet Parasitol*. 2009;165:96–108.
162. Bygarski EE, Prichard RK, Ardelli BF. Resistance to the macrocyclic lactone moxidectin is mediated in part by membrane transporter P-glycoproteins: implications for control of drug resistant parasitic nematodes. *Int J Parasitol Drugs Drug Resist*. 2014;4:143–151.
163. Janko C, Geyer J. Moxidectin has a lower neurotoxic potential but comparable brain penetration in P-glycoprotein-deficient CF-1 mice compared to ivermectin. *J Vet Pharmacol Ther*. 2013;36:275–284.
164. Menez C, Sutra JF, Prichard R, et al. Relative neurotoxicity of ivermectin and moxidectin in Mdr1ab (-/-) mice and effects on mammalian GABA(A) channel activity. *PLoS Negl Trop Dis*. 2012;6:e1883.
165. Godoy P, Che H, Beech RN, et al. Characterization of *Haemonchus contortus* P-glycoprotein-16 and its interaction with the macrocyclic lactone anthelmintics. *Mol Biochem Parasitol*. 2015;204:11–15.
166. Korth-Bradley JM, Parks V, Chalon S, et al. The effect of a high-fat breakfast on the pharmacokinetics of moxidectin in healthy male subjects: a randomized phase I trial. *Am J Trop Med Hyg*. 2012;86:122–125.
167. Opoku NO, Bakajika DK, Kanza EM, et al. Single dose moxidectin versus ivermectin for *Onchocerca volvulus* infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial. *Lancet*. 2018;392:1207–1216.
168. Awadzi K, Opoku NO, Attah SK, et al. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin in *Onchocerca volvulus* infection. *PLoS Negl Trop Dis*. 2014;8:e2953.
169. United States Food & Drug Administration. Drug Trials Snapshots: Moxidectin—Prescribing information 13 June 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf.
170. Korth-Bradley JM, Parks V, Chalon S, et al. Excretion of moxidectin into breast milk and pharmacokinetics in healthy lactating women. *Antimicrob Agents Chemother*. 2011;55:5200–5204.
171. Korth-Bradley JM, Parks V, Wagner F, et al. Effect of moxidectin on CYP3A4 activity as evaluated by oral midazolam pharmacokinetics in healthy subjects. *Clin Pharmacol Drug Dev*. 2013;3:151–157.
172. Cesbron JY, Capron A, Vargaftig BB, et al. Platelets mediate the action of diethylcarbamazine on microfilariae. *Nature*. 1987;325:533–536.
173. Liu LX, Weller PF. Intravascular filarial parasites inhibit platelet aggregation. Role of parasite-derived prostanoids. *J Clin Invest*. 1992;89:1113–1120.
174. Maizels RM, Denham DA. Diethylcarbamazine (DEC): immunopharmacological interactions of an anti-filarial drug. *Parasitology*. 1992;105(suppl):S49–S60.
175. Fujimaki Y, Ehara M, Kimura E, et al. Diethylcarbamazine, antifilarial drug, inhibits microtubule polymerization and disrupts preformed microtubules. *Biochem Pharmacol*. 1990;39:851–856.
176. Edwards G, Breckenridge AM, Adjepon-Yamoah KK, et al. The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol*. 1981;12:807–812.
177. Adjepon-Yamoah KK, Edwards G, Breckenridge AM, et al. The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol*. 1982;13:829–834.
178. Orme M, Edwards G, Awadzi K, et al. Clinical pharmacokinetics of drugs against onchocerciasis. *Acta Leiden*. 1990;59:329–342.
179. Joseph CA, Dixon PA. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol*. 1984;36:281–282.
180. Eberhard ML, Lammie PJ, Dickinson CM, et al. Evidence of nonsusceptibility to diethylcarbamazine in Wuchereria bancrofti. *J Infect Dis*. 1991;163:1157–1160.
181. Eberhard ML, Lowrie RC Jr, Lammie PJ. Persistence of microfilaremia in bancroftian filariasis after diethylcarbamazine citrate therapy. *Trop Med Parasitol*. 1988;39:128–130.
182. Noroes J, Dreyer G, Santos A, et al. Assessment of the efficacy of diethylcarbamazine on adult Wuchereria bancrofti in vivo. *Trans R Soc Trop Med Hyg*. 1997;91:78–81.
183. Nutman TB, Miller KD, Mulligan M, et al. Diethylcarbamazine prophylaxis for human loiasis. Results of a double-blind study. *N Engl J Med*. 1988;319:752–756.
184. Bryceson AD, Warrell DA, Pope HM. Dangerous reactions to treatment of onchocerciasis with diethylcarbamazine. *Br Med J*. 1977;1:742–744.
185. Bird AC, el Sheikh H, Anderson J, et al. Changes in visual function and in the posterior segment of the eye during treatment of onchocerciasis with diethylcarbamazine citrate. *Br J Ophthalmol*. 1980;64:191–200.
186. Dreyer G, Pires ML, de Andrade LD, et al. Tolerance of diethylcarbamazine by microfilaraemic and amicrofilaraemic individuals in an endemic area of bancroftian filariasis, Recife, Brazil. *Trans R Soc Trop Med Hyg*. 1994;88:232–236.
187. Carme B, Boulesteix J, Boutes H, et al. Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. *Am J Trop Med Hyg*. 1991;44:684–690.
188. Taylor MJ, Bandi C, Hoerauf A. *Wolbachia* bacterial endosymbionts of filarial nematodes. *Adv Parasitol*. 2005;60:245–284.
189. Hoerauf A, Buttner DW, Adjei O, et al. Onchocerciasis. *BMJ*. 2003;326:207–210.
190. Supali T, Djuardi Y, Pfarr KM, et al. Doxycycline treatment of *Brugia malayi*-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. *Clin Infect Dis*. 2008;46:1385–1393.
191. Gayen P, Nayak A, Saini P, et al. A double-blind controlled field trial of doxycycline and albendazole in combination for the treatment of bancroftian filariasis in India. *Acta Trop*. 2013;125:150–156.
192. Keiser J, Tritten L, Silbereisen A, et al. Activity of oxantel pamoate monotherapy and combination chemotherapy against *Trichuris muris* and hookworms: revival of an old drug. *PLoS Negl Trop Dis*. 2013;7:e2119.
193. Aubry ML, Cowell P, Davey MJ, et al. Aspects of the pharmacology of a new anthelmintic: pyrantel. *Br J Pharmacol*. 1970;38:332–344.
194. Robertson AP, Bjorn HE, Martin RJ. Pyrantel resistance alters nematode nicotinic acetylcholine receptor single-channel properties. *Eur J Pharmacol*. 2000;394:1–8.
195. Kopp SR, Coleman GT, Traub RJ, et al. Acetylcholine receptor subunit genes from *Ancylostoma caninum*: altered transcription patterns associated with pyrantel resistance. *Int J Parasitol*. 2009;39:435–441.
196. Kimura Y, Kume M. Absorption, distribution, excretion and metabolism of pyrantel pamoate. *Pharmacometrics*. 1971;5:347–358.
197. Cervoni WA, Oliver-Gonzalez J. Clinical evaluation of pyrantel pamoate in helminthiasis. *Am J Trop Med Hyg*. 1971;20:589–591.
198. Loria P, Miller S, Foley M, et al. Inhibition of the peroxidative degradation of haem as the basis of action of chloroquine and other quinoline antimalarials. *Biochem J*. 1999;339(Pt 2):363–370.
199. Terada M, Fujiu Y, Sano M. Studies on chemotherapy of parasitic helminths (XVII). Effects of pyrantel on the motility of various parasitic helminths and isolated host tissues. *Experientia*. 1983;39:1020–1022.
200. Farid Z, Bassily S, Miner WF, et al. Comparative single/dose treatment of hookworm and roundworm infections with levamisole, pyrantel and bephenium. *J Trop Med Hyg*. 1977;80:107–108.
201. Holland CV, O'Shea E, Asaolu SO, et al. A cost-effectiveness analysis of anthelminthic intervention for community control of soil-transmitted helminth infection: levamisole and *Ascaris lumbricoides*. *J Parasitol*. 1996;82:527–530.
202. Martin RJ, Robertson AP, Bjorn H. Target sites of anthelmintics. *Parasitology*. 1997;114(suppl):S111–S124.
203. Atchison WD, Geary TG, Manning B, et al. Comparative neuromuscular blocking actions of levamisole and pyrantel-type anthelmintics on rat and gastrointestinal nematode somatic muscle. *Toxicol Appl Pharmacol*. 1992;112:133–143.
204. Robertson AP, Bjorn HE, Martin RJ. Resistance to levamisole resolved at the single-channel level. *FASEB J*. 1999;13:749–760.
205. Graziani G, de Martin GL. Pharmacokinetic studies on levamisole on the pharmacokinetics and relative bioavailability of levamisole in man. *Drugs Exp Clin Res*. 1977;2:235–240.
206. Adams JG. Pharmacokinetics of levamisole. *J Rheumatol Suppl*. 1978;4:137–142.
207. Edwards G, Breckenridge AM. Clinical pharmacokinetics of anthelmintic drugs. *Clin Pharmacokinet*. 1988;15:67–93.
208. Robertson AP, Puttachary S, Buxton SK, et al. Tribendimidine: mode of action and nAChR subtype selectivity in *Ascaris* and *Oesophagostomum*. *PLoS Negl Trop Dis*. 2015;9:e0003495.
209. Xiao SH, Utzinger J, Tanner M, et al. Advances with the Chinese anthelminthic drug tribendimidine in clinical trials and laboratory investigations. *Acta Trop*. 2013;126:115–126.
210. Duthaler U, Sayasone S, Vanobbergen F, et al. Single-ascending-dose pharmacokinetic study of tribendimidine in *Opisthorchis viverrini*-infected patients. *Antimicrob Agents Chemother*. 2016;60:5705–5715.
211. Vanobberghen F, Penny MA, Duthaler U, et al. Population pharmacokinetic modeling of tribendimidine metabolites in *Opisthorchis viverrini*-infected adults. *Antimicrob Agents Chemother*. 2016;60:5695–5704.
212. Yuan G, Zhang R, Wei C, et al. Effects of food on the pharmacokinetics of tribendimidine enteric-coated tablet in healthy Chinese subjects. *Lat Am J Pharm*. 2015;34:967–972.
213. Steinmann P, Zhou XN, Du ZW, et al. Tribendimidine and albendazole for treating soil-transmitted helminths, *Strongyloides stercoralis* and *Taenia* spp.: open-label randomized trial. *PLoS Negl Trop Dis*. 2008;2:e322.
214. Moser W, Coulibaly JT, Ali SM, et al. Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Cote d'Ivoire: a randomised, controlled, single-blinded, non-inferiority trial. *Lancet Infect Dis*. 2017;17:1162–1171.
215. Brindley PJ, Sher A. The chemotherapeutic effect of praziquantel against *Schistosoma mansoni* is dependent on host antibody response. *J Immunol*. 1987;139:215–220.
216. Gryseels B, Stelma FF, Talla I, et al. Epidemiology, immunology and chemotherapy of *Schistosoma mansoni* infections in a recently exposed community in Senegal. *Trop Geogr Med*. 1994;46(4 Spec No):209–219.
217. Xiao SH, Friedman PA, Catto BA, et al. Praziquantel-induced vesicle formation in the tegument of male *Schistosoma mansoni* is calcium dependent. *J Parasitol*. 1984;70:177–179.
218. Fallon PG, Sturrock RF, Niang AC, et al. Short report: diminished susceptibility to praziquantel in a Senegal isolate of *Schistosoma mansoni*. *Am J Trop Med Hyg*. 1995;53:61–62.
219. Ismail M, Metwally A, Farghaly A, et al. Characterization of isolates of *Schistosoma mansoni* from Egyptian villagers that tolerate high doses of praziquantel. *Am J Trop Med Hyg*. 1996;55:214–218.
220. Liang YS, Coles GC, Dai JR, et al. Biological characteristics of praziquantel-resistant and -susceptible isolates of *Schistosoma mansoni*. *Ann Trop Med Parasitol*. 2001;95:715–723.
221. William S, Botros S, Ismail M, et al. Praziquantel-induced tegumental damage in vitro is diminished in schistosomes derived from praziquantel-resistant infections. *Parasitology*. 2001;122(Pt 1):63–66.
222. Pinto-Almeida A, Mendes T, Armada A, et al. The role of efflux pumps in *Schistosoma mansoni* praziquantel resistant phenotype. *PLoS ONE*. 2015;10:e0140147.

223. Lovis L, Mak TK, Phongluxa K, et al. Efficacy of praziquantel against *Schistosoma mekongi* and *Opisthorchis viverrini*: a randomized, single-blinded dose-comparison trial. *PLoS Negl Trop Dis*. 2012;6:e1726.
224. Patzschke K, Putter J, Wegner LA, et al. Serum concentrations and renal excretion in humans after oral administration of praziquantel—results of three determination methods. *Eur J Drug Metab Pharmacokinet*. 1979;4:149–156.
225. Putter J, Held F. Quantitative studies on the occurrence of praziquantel in milk and plasma of lactating women. *Eur J Drug Metab Pharmacokinet*. 1979;4:193–198.
226. Bittencourt PR, Gracia CM, Martins R, et al. Phenytoin and carbamazepine decreased oral bioavailability of praziquantel. *Neurology*. 1992;42(3 Pt 1):492–496.
227. Vazquez ML, Jung H, Sotelo J. Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. *Neurology*. 1987;37:1561–1562.
228. Pehrson PO, Bengtsson E, Diekmann HW, et al. Treatment with praziquantel in a patient with schistosomiasis and chronic renal failure. *Trans R Soc Trop Med Hyg*. 1983;77:687–688.
229. Watt G, White NJ, Padre L, et al. Praziquantel pharmacokinetics and side effects in *Schistosoma japonicum*-infected patients with liver disease. *J Infect Dis*. 1988;157:530–535.
230. Montero R, Ostrosky P. Genotoxic activity of praziquantel. *Mutat Res*. 1997;387:123–139.
231. Olveda RM, Acosta LP, Tallo V, et al. Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2016;16:199–208.
232. Matsumoto J. Adverse effects of praziquantel treatment of *Schistosoma japonicum* infection: involvement of host anaphylactic reactions induced by parasite antigen release. *Int J Parasitol*. 2002;32:461–471.
233. Polderman AM, Gryseels B, Gerold JL, et al. Side effects of praziquantel in the treatment of *Schistosoma mansoni* in Maniema, Zaire. *Trans R Soc Trop Med Hyg*. 1984;78:752–754.
234. Chen MG, Fu S, Hua XJ, et al. A retrospective survey on side effects of praziquantel among 25,693 cases of schistosomiasis japonica. *Southeast Asian J Trop Med Public Health*. 1983;14:495–500.
235. Nash TE, Cheever AW, Ottesen EA, et al. Schistosome infections in humans: perspectives and recent findings. NIH conference. *Ann Intern Med*. 1982;97:740–754.
236. Kaye B, Woolhouse NM. The metabolism of oxamniquine—a new schistosomicide. *Ann Trop Med Parasitol*. 1976;70:323–328.
237. Daneshmend TK, Homeida MA. Oxamniquine pharmacokinetics in hepatosplenic schistosomiasis in the Sudan. *J Antimicrob Chemother*. 1987;19:87–93.
238. Kokwaro GO, Taylor G. Oxamniquine pharmacokinetics in healthy Kenyan African volunteers. *East Afr Med J*. 1991;68:359–364.
239. Cioli D, Pica-Mattoccia L, Archer S. Antischistosomal drugs: past, present … and future? *Pharmacol Ther*. 1995;68:35–85.
240. Al-Aska AK. Treatment of *Schistosoma mansoni* infection with oxamniquine in Riyadh, Saudi Arabia. *Trop Med Parasitol*. 1985;36:213–214.
241. Krajden S, Keystone JS, Glenn C. Safety and toxicity of oxamniquine in the treatment of *Schistosoma mansoni* infections, with particular reference to electroencephalographic abnormalities. *Am J Trop Med Hyg*. 1983;32:1344–1346.
242. Stokvis H, Bauer AG, Stuiver PC, et al. Seizures associated with oxamniquine therapy. *Am J Trop Med Hyg*. 1986;35:330–331.
243. Masimirembwa CM, Hasler JA, Johansson I. Inhibitory effects of antiparasitic drugs on cytochrome P450 2D6. *Eur J Clin Pharmacol*. 1995;48:35–38.
244. Forsyth DM, Rashid C. Treatment of urinary schistosomiasis. Practice and theory. *Lancet*. 1967;1:130–133.
245. Feldmeier H, Doehring E. Clinical experience with metrifonate. Review with emphasis on its use in endemic areas. *Acta Trop*. 1987;44:357–368.
246. Snellen WM. Therapeutic properties of metrifonate. *Acta Pharmacol Toxicol (Copenh)*. 1981;49(suppl 5): 114–117.
247. Danso-Appiah A, Utzinger J, Liu J, et al. Drugs for treating urinary schistosomiasis. *Cochrane Database Syst Rev*. 2008;(3):CD000053.
248. Davis RP, Bailey DR. Effect of metrifonate on blood cholinesterases in children during the treatment of schistosomiasis. *Bull World Health Organ*. 1972;46: 747–759.
249. Feldmeier H, Chitsulo L. Therapeutic and operational profiles of metrifonate and praziquantel in *Schistosoma haematobium* infection. *Arzneimittelforschung*. 1999;49:557–565.
250. Cioli D. Praziquantel: is there real resistance and are there alternatives? *Curr Opin Infect Dis*. 2000;13:659–663.
251. Holmstedt B, Nordgren I, Sandoz M, et al. Metrifonate. Summary of toxicological and pharmacological information available. *Arch Toxicol*. 1978;41:3–29.
252. Davis A, Bailey DR. Metrifonate in urinary schistosomiasis. *Bull World Health Organ*. 1969;41:209–224.
253. Aden-Abdi Y, Villen T, Ericsson O, et al. Metrifonate in healthy volunteers: interrelationship between pharmacokinetic properties, cholinesterase inhibition and side-effects. *Bull World Health Organ*. 1990;68:731–736.
254. Heinig R, Sachse R. The effect of food and time of administration on the pharmacokinetic and pharmacodynamic profile of metrifonate. *Int J Clin Pharmacol Ther*. 1999;37:456–464.
255. Pearson RD, Hewlett EL. Niclosamide therapy for tapeworm infections. *Ann Intern Med*. 1985;102:550–551.
256. Zumaquero-Rios JL, Sarracent-Perez J, Rojas-Garcia R, et al. Fascioliasis and intestinal parasitoses affecting schoolchildren in Atlixco, Puebla State, Mexico: epidemiology and treatment with nitazoxanide. *PLoS Negl Trop Dis*. 2013;7:e2553.
257. Bassiouny HK, Soliman NK, el Daly SM, et al. Human fascioliasis in Egypt: effect of infection and efficacy of bithionol treatment. *J Trop Med Hyg*. 1991;94:333–337.
258. Singh TS, Mutim SS, Razaque MA. Pulmonary paragonimiasis: clinical features, diagnosis, and treatment of 39 cases in Manipur. *Trans R Soc Trop Med Hyg*. 1986;80:967–971.
259. Yokogawa M, Iwasaki M, Shigeyasu M, et al. Chemotherapy of paragonimiasis with bithionol. V. Studies on the minimum effective dose and changes in abnormal x-ray shadows in the chest after treatment. *Am J Trop Med Hyg*. 1963;12:859–869.
260. Farag HF, Salem A, el Hifni SA, et al. Bithionol (Bitin) treatment in established fascioliasis in Egyptians. *J Trop Med Hyg*. 1988;91:240–244.
261. Bacq Y, Besnier JM, Duong TH, et al. Successful treatment of acute fascioliasis with bithionol. *Hepatology*. 1991;14:1066–1069.

44 Antiviral Agents: General Principles

Raphael Dolin and Janet Morgan

Although viruses are among the most common causes of human illnesses, the development of antiviral drugs to treat or prevent viral infections has historically lagged behind the development of drugs against other microbial agents. In part, this has been related to difficulties in detection and characterization of many viruses, and in limitations in techniques for evaluation of laboratory and clinical effects of antiviral agents. However, in recent years the development of antiviral chemotherapy and chemoprophylaxis has markedly expanded, driven in large part by advances in understanding of molecular virology and viral pathogenesis and by the establishment of highly specific, sensitive, and quantitative methods for viral detection. More than 70 antiviral agents are now available to treat various viral infections, including 28 to treat human immunodeficiency virus (HIV) infections (see Chapter 128), and many additional agents are at various stages of preclinical and clinical development. The availability of laboratory data to guide administration of antiviral drugs and to assess their clinical efficacy has also been limited compared with data used in treatment of bacterial infections. However, exemplified by the success of antiviral therapy for HIV and hepatitis B and C virus infections, methods have now become widely available to assess sensitivity of viruses to antiviral drugs, to quantitate viruses in host compartments (virus load), and to determine pharmacokinetics of antiviral drugs. These methods now provide data to guide the appropriate use of antiviral agents.

General principles for the use of antiviral agents are discussed in this chapter. Individual antiviral agents are reviewed in Chapters 45 through 48, and antiretroviral therapy is reviewed in Chapter 128.

MECHANISMS OF ACTION OF ANTIVIRAL AGENTS

The mechanisms of action of antiviral agents generally involve inhibition of a virus-specific step in viral replication. Because viral replication depends primarily on host cell metabolic functions, useful antiviral agents should inhibit virus-specific functions but leave host cell functions intact, or at least preferentially inhibit virus-directed as opposed to host cell–directed macromolecular synthesis. In consequence, antiviral agents typically have a restricted spectrum of activity. Although many compounds can be found that exhibit antiviral activity in vitro, most also affect host cell functions and are associated with low therapeutic ratios or with unacceptable toxicity in humans. Most current antiviral agents inhibit ongoing viral replication and then enable host defenses to eliminate the virus. If "viable" virus persists after the drug is removed, virus replication may resume. Viruses that have established a latent, that is, a nonreplicating, state are generally not affected by currently available antiviral agents.

The search for effective and specific antiviral agents has identified specific cellular sites and macromolecular mechanisms whose interdiction can be used to inhibit virus replication. The individual mechanisms of action through which individual drugs exert their antiviral effects are discussed as follows.

Inhibition of Viral Nucleic Acid Synthesis

Many antiviral compounds are nucleoside or nucleotide analogues whose mechanism of action is inhibition of viral nucleic acid synthesis. Nucleoside analogues such as acyclovir and penciclovir require phosphorylation to the monophosphate, which requires a thymidine kinase coded by herpes simplex virus and not present in uninfected cells.[1] Cellular kinases phosphorylate acyclovir to the triphosphate moiety, which inhibits the viral DNA polymerase and is incorporated into viral DNA as a chain terminator, thus inhibiting viral DNA synthesis. The requirement for a virus-encoded enzyme provides a virus-specific mechanism of action. Herpes simplex viruses that lack a thymidine kinase are resistant to acyclovir and penciclovir.[2]

Cidofovir is a monophosphorylated nucleotide analogue that does not require a virus-coded thymidine kinase for its activity. It uses cellular kinases to convert it to a diphosphate moiety that inhibits viral DNA polymerase and also causes premature chain termination. It is active against viruses that lack thymidine kinase and are therefore resistant to acyclovir and penciclovir.[3]

Foscarnet is not a nucleoside or nucleotide analogue but, rather, a pyrophosphate that blocks the pyrophosphate-binding site on the viral DNA polymerase. Thus it does not require intracellular metabolism for its antiherpesvirus activity.[4]

A novel mechanism of action, inhibition of the helicase-primase complex, is manifested by amenamevir[5] and pritelivir,[6] which are active against herpes simplex viruses types 1 and 2. The helicase-primase complex is a heterotrimer consisting of helicase, primase, and cofactor subunits that are essential for DNA replication. Amenamevir and pritelivir are not nucleoside analogues, do not require phosphorylation by thymidine kinase, and are therefore active against viruses that are resistant to acyclovir and penciclovir because of thymidine kinase deficiencies. Amenamevir and pritelivir are undergoing clinical studies in suppression and treatment of genital herpes (see Chapter 46).

Letermovir is an antiviral agent with activity against cytomegalovirus (CMV) through inhibition of the viral terminase enzyme complex, which results in interference with processing and blockage of viral DNA.[7] It does not inhibit the viral DNA polymerase and is therefore active against CMV strains resistant to ganciclovir, cidofovir, and foscarnet.

In HIV infection nucleoside and nucleotide analogues inhibit viral complementary DNA (cDNA) synthesis through inhibition of reverse transcriptase. These drugs must be phosphorylated to the triphosphate moieties for anti-HIV activity. They include zidovudine, tenofovir, emtricitabine, and abacavir. Nonnucleoside reverse-transcriptase inhibitors (NNRTIs) also bind to reverse transcriptase but do so in a pocket far from the active site, in contrast to the nucleoside and nucleotide analogues. NNRTIs include nevirapine,[8] efavirenz, and rilpivirine.[9]

Integrase Strand Inhibitors

In HIV infection HIV RNA is reverse transcribed in the cytoplasm, and the cDNA is processed by HIV integrase and transported to the nucleus, where integration into the cellular genome occurs through strand transfer, which is blocked by integrase strand inhibitors (INSTIs).[10] Raltegravir, elvitegravir, and dolutegravir are examples of INSTIs. The high efficacy and safety of INSTIs is reflected in their inclusion in currently recommended first-line treatment regimens (see Chapter 128).

CAP-Dependent Endonuclease Inhibitor

Viral RNA transcription in influenza viruses requires a cap dependent endonuclease (CEN), which provides "cap-snatching" activity and primes viral transcription. CEN resides on the N-terminal domain of the polymerase acid (PA) subunit of the RNA-dependent RNA polymerase

of influenza A viruses and is highly conserved among influenza A subtypes. Baloxavir marboxil is a small-molecule inhibitor of influenza A and B CENs. It has recently been shown to be effective in both clinical and virologic parameters in a phase III study of influenza A and B infections.[11–13]

RNA Antisense Nucleotides

Antisense nucleotides inhibit transcription of messenger (m)RNA and can be used to inhibit replication of viruses. Fomivirsen is an antisense oligonucleotide that is complementary to a sequence in mRNA transcripts of the major immediate-early region 2 of CMV.[14] It is administered intravitreally to treat cytomegaloviral retinitis in HIV-infected patients who have failed or are intolerant to other treatments. Because of its unique antiviral mechanism of action, fomivirsen is active against cytomegaloviral strains that are resistant to ganciclovir, foscarnet, or cidofovir. Currently, fomivirsen production has been discontinued and is no longer available in the United States.

Viral Entry Inhibition

Inhibition of attachment of virus to its cellular receptor or subsequent intracellular entry of virus is an important mechanism for antiviral activity. Maraviroc is an allosteric inhibitor that interferes with attachment of HIV-1 glycoprotein (gp)120 to the CCR5 cellular chemokine receptor.[15,16] Enfuvirtide is a synthetic peptide that inhibits gp41-mediated fusion of HIV-1 with the cell membrane and thus blocks virus entry[17] (see Chapter 128).

Protease Inhibition

Many viruses require proteolytic cleavage of polypeptide precursors to activate essential viral proteins. HIV-1 and HIV-2 contain aspartyl proteases that cleave Gag and Gag-Pol polyproteins into essential structural and enzymatic components. Viral particles may still be found in the presence of protease inhibitors, but such particles are rendered noninfectious. For HIV-1, there are 10 clinically used inhibitors of such protease activity, which are important components of combination antiretroviral regimens. These protease inhibitors include ritonavir, darunavir, and atazanavir. Ritonavir is a protease inhibitor that is used at lower doses, primarily to increase the bioavailability and half-life of other protease inhibitors, except for nelfinavir.

Hepatitis C has a polyprotein in which regions contain proteins NS3, NS4A, NS4B, NS5A, and NS5B, which are required for RNA replication and assemble into a membrane-associated replicase complex within the cytoplasm of infected cells. Multiple direct-acting antivirals (DAAs) are available that inhibit the just-mentioned proteins, including NS3/NS4A proteases and NS5A and NS5B proteins, and they have pangenotype activity (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir).[18]

Inhibition of Virus Uncoating

The adamantane compounds amantadine[19] and rimantadine[20] interfere with the function of the M2 protein of influenza A virus and inhibit uncoating of influenza virus shortly after entry of virus into cells.[19,20] Single amino-acid changes can render viruses resistant to the adamantanes, as is the case with currently circulating (2013–17) influenza A viruses.[21]

Inhibition of Virus Release

The neuraminidase inhibitors oseltamivir, zanamivir, and peramivir interfere with release of influenza A and B from infected cells.[22–24] Neuraminidase prevents the clumping of released virus, and thus inhibition of this enzyme retards the cell-to-cell movement of virus.

MODIFIERS OF HOST DEFENSES AGAINST VIRUSES

Appropriate host defenses, including both innate and adaptive immune responses, are essential for prevention and recovery from viral infection. Immunosuppression resulting from organ transplantation, cancer chemotherapy, or HIV infection may be associated with more severe viral infections and with higher rates of recrudescent or chronic viral infections. Antiviral prophylaxis and preemptive therapy have become standard practice in immunocompromised patients, such as hematopoietic stem cell and solid-organ transplant recipients. Responses to antiviral treatment may be delayed in such patients, and the risk for selecting drug-resistant viruses is higher. In addition, some antiviral agents may blunt host immune responses through reductions in viral antigens that would otherwise stimulate such responses. Reduction of immunosuppression should be part of antiviral treatment in immunocompromised patients whenever possible.

Interferons

Interferons are cytokines that do not directly have antiviral activity themselves but induce an antiviral state in host cells through activation of tyrosine kinases (Tyk2, JAK1, JAK2) and phosphorylation of cytoplasmic signal transducer and activator of transcription (STAT) proteins (see Chapter 48). This results in inhibition of multiple steps in viral replication, depending on the particular virus and cell type.[25,26] Interferons have been most widely used in treatment of hepatitis B and C virus infections as part of combination regimens with ribavirin and with protease inhibitors for hepatitis C. Interferon therapy is no longer recommended for treatment of hepatitis C (see Chapter 47).

Innate Immunity Stimulators

Imiquimod is an imidazoquinoline that is a Toll-like receptor (TLR) 7 agonist that activates various cells in the innate immune system.[27] It is topically administered and is approved for treatment of anogenital warts (see Chapter 48). Resiquimod is a structurally related investigational compound that is a TLR7 and TLR8 agonist.[28]

Host Sialidases

Influenza and parainfluenza viruses infect host cells through binding with sialic acid cell receptors. Host sialidases inactivate such receptors and reduce viral infection through inhibition of virus binding. DAS181 is a sialidase attached to a respiratory epithelium–binding domain that has activity against influenza A and B and parainfluenza virus infections in vitro and in vivo.[29] It is being evaluated in clinical studies in influenza and parainfluenza infections in immunosuppressed patients (see Chapter 45).

DETERMINATION OF SENSITIVITY OF VIRUSES TO ANTIVIRAL AGENTS

Determination of the sensitivity of viruses to antiviral agents is essential for appropriate use of antiviral chemotherapy or chemoprophylaxis, just as it has been for use of antibacterials. Sensitive and specific laboratory assays to determine activity of antivirals are now increasingly available, both as licensed, commercial assays as well as in research settings. For certain viral infections for which antivirals are available, epidemiologic-based sensitivity data are widely available, generally through public health agencies, which can guide selection of antivirals. Examples of these are infections with influenza virus, herpes simplex virus, varicella-zoster virus, and hepatitis C virus. For others, such as HIV infection, determination of viral sensitivities may be important in selection of an initial regimen or in its modification.

Originally, laboratory assays of sensitivity to antiviral agents were based entirely on phenotypic assays in cell culture developed for individual viruses.[30] Results in these assays varied with the in vitro system that was used and were often difficult to standardize. These assays are now being largely supplanted by highly sensitive, rapid, and specific molecular genotypic assays (see Chapter 16), in which specific amino-acid changes have been associated with phenotypic resistance.[31] Genotypic assays can detect thymidine kinase mutations, which are associated with resistance to acyclovir and penciclovir in herpes simplex virus and varicella-zoster virus infections. Mutations in phosphotransferase and DNA polymerase genes of CMV are associated with resistance to ganciclovir, cidofovir, and foscarnet. Despite their advantages, genotypic assays rely only on mutations that have been previously recognized to be associated with phenotypic resistance. Thus the probes that are used must be frequently updated to detect newly recognized mutations that are associated with antiviral resistance. In situations in which de novo resistance is uncommon, such as herpes simplex virus or varicella-zoster virus infections in normal hosts, genotypic assays